

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-014**

**CLINICAL PHARMACOLOGY and**  
**BIOPHARMACEUTICS REVIEW(S)**

NDA: 21-014	REVIEWER: Vanitha J. Sekar, Ph.D.
DRUG: Oxcarbazepine (Trileptal™)	TEAM LEADER: Chandra Sahajwalla, Ph.D.
FORMULATION(S): 150, 300, 600 mg tablets	SUBMISSION DATE: September 25, 1998
APPLICANT: Novartis	

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## SYNOPSIS

Oxcarbazepine (OXC), the keto-analog of carbamazepine, is an orally active anticonvulsant that is presently registered in 47 countries. OXC is rapidly reduced by cytosolic enzymes to a monohydroxylated derivative (MHD) which is pharmacologically active. The applicant is seeking approval of oxcarbazepine (Trileptal™) tablets in the USA for oral administration.

Film-coated tablets (150, 300 and 600 mg strengths) were developed as the final dosage form of OXC to be marketed in the USA. The pivotal bioequivalence study was conducted using the highest strength (600 mg) of the final market image formulation. Following single and multiple doses, under fed conditions, the 600 mg to-be-marketed tablet was found to be bioequivalent to the pivotal trial formulation. Food did not have an effect on the bioavailability of the final market formulation (600 mg), whereas the non-US current market formulation was shown to have a significant food effect. The applicant's request for a waiver of a bioequivalence study for the two lower strengths of Trileptal (150 and 300 mg) is based upon comparable multi-media dissolution profiles, compositional proportionality of the 3 strengths of OXC tablets and high permeability ( $F > 95\%$ ) of the drug, which is acceptable.

Trileptal is recommended for use either as monotherapy or in combination with other antiepileptic drugs. In mono- and adjunctive therapy, the applicant recommends treatment with Trileptal to be initiated at a dose of 600 mg/day (8-10 mg/kg/day) given in two divided doses. The dose may be increased depending on the clinical response of the patient. Doses of up to 4200 mg/day have been administered in a limited number of patients in order to achieve a maximum therapeutic effect. Drug plasma level monitoring is not a recommendation for Trileptal.

Mass balance studies showed that most of the dose (over 94%) was renally excreted as monohydroxy (MHD) and less than 5% was excreted in the feces, suggesting that OXC is almost completely absorbed from the gastrointestinal tract. Very low (approximately 2%) concentrations of OXC were present in plasma. OXC was rapidly converted to a high extent to the 10-monohydroxy metabolite. MHD accounted for over 65% of the total AUC in plasma. The second metabolite CGP 10000 (trans dihydroxy derivative) was also present in low concentrations in plasma.

At therapeutic concentrations, OXC was moderately bound to serum proteins (76%), whereas binding of MHD was low (40%). Albumin was the major protein responsible for binding to serum proteins for OXC and MHD. Binding of OXC and MHD to gamma globulin and AAG was negligible.

Pharmacokinetic studies showed that following oral administration of Trileptal, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). After single dose administration of 600 mg Trileptal to healthy male volunteers under fasted conditions, the mean  $C_{max}$  value of MHD was  $34 \mu\text{mol/L}$  ( $8.65 \mu\text{g/mL}$ ), with a corresponding median  $t_{max}$  of 4.5 hours. Steady-state plasma concentrations of MHD are reached within 2-3 days in patients when Trileptal is given twice a day. At steady-state the pharmacokinetics of MHD are linear and show dose proportionality across the dose range of 300 to 2400 mg/day. Comparison of results from single dose pharmacokinetic studies to multiple dose studies indicated that there was a greater than 3-fold accumulation of MHD following multiple dosing.

Comparison of the pharmacokinetic parameters for MHD between young and elderly volunteers indicated that the exposure and peak concentrations of MHD were significantly higher (30 to 60%) in the elderly compared to young volunteers, after multiple doses of OXC. Comparisons of creatinine clearance in young and elderly volunteers indicated that the difference was due to age-related reductions in creatinine clearance.

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When Trileptal is administered as a single 300 mg dose, to renally impaired patients (creatinine clearance < 30 mL/min), the elimination half-life of MHD is prolonged with a corresponding two fold increase in AUC. The recommended dose for Trileptal in these patients is to initiate dosing at one-half the usual starting doses (300 mg/day) and increase, if necessary, using a slower rate until the desired clinical response is achieved.

The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects. Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. No dose adjustment is recommended in the patients. The pharmacokinetics of OXC and MHD have not been evaluated in severe hepatic impairment.

The systemic exposure to MHD was reduced in children compared to adults given the same dosing regimen. In children aged 2-6 years, the mean specific trough concentration (dose corrected trough concentration) was about 50 to 60% lower than in adults; in children aged 6-14 years, the mean specific trough concentration was about 30 to 40% lower than in adults. The proposed dosing regimen for children older than 2 years is the same as that proposed in adults: starting dose of 8-10 mg/kg/day as 2 divided doses and if clinically indicated, dose may be increased by a maximum increment of 10 mg/kg/day at weekly intervals from the starting dose to a maximum dose of 46 mg/kg/day. The dose is recommended based on the fact that therapeutic effects were observed at a median maintenance dose of OXC at 30 mg/kg/day as adjunctive therapy. Also, therapeutic benefit was observed in majority of the patients at a maintenance dose of 15-25 mg/kg/day in a monotherapy trial with OXC.

*In vitro* and *in vivo* studies demonstrate that Trileptal has a low potential for drug interactions. Oxcarbazepine was evaluated in human liver microsomes to determine its capacity to inhibit the major cytochrome P450 enzymes responsible for the metabolism of other drugs. Results demonstrate that oxcarbazepine and its pharmacologically active 10-monohydroxy metabolite (MHD) have little capacity to function as inhibitors for most of the human cytochrome P450 enzymes evaluated (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11) with the exception of CYP2C19 and CYP 3A4/5. Both OXC and MHD were observed to competitively inhibit CYP 2C19 with  $K_i$  values of 228  $\mu$ M and 88  $\mu$ M, respectively. CYP 3A4/5 was found to be inhibited both by OXC (non-competitive) and MHD (competitive) at  $K_i$  values of 279  $\mu$ M and 647  $\mu$ M, respectively. The mean steady state trough plasma concentrations of MHD following 1200 mg bid dose of OXC is approximately 108  $\mu$ M in patients and  $C_{max}$  following a 1200 mg dose was approximately 50  $\mu$ M. Comparing these pharmacokinetic parameters to the  $K_i$  values suggest that while inhibition of CYP 3A4/4 by OXC and MHD may not have clinical significance, the inhibition of CYP 2C19 substrates by OXC and MHD may be clinically relevant. Therefore, interactions could arise when co-administering high doses of Trileptal with drugs that are metabolized by CYP2C19 (e.g. phenobarbital, phenytoin). *In vitro*, the UDP-glucuronyl transferase level was increased, indicating induction of this enzyme. Increases of 22% with MHD and 47% with oxcarbazepine were observed. As MHD is only a weak inducer of UDP-glucuronyl transferase, it is unlikely to have an effect on drugs which are mainly eliminated by conjugation through UDP-glucuronyl transferase (e.g., valproic acid, lamotrigine). In addition, oxcarbazepine and MHD induce a subgroup of the cytochrome P450 3A family (CYP3A4 and CYP3A5).

Potential interactions between Trileptal and other AEDs were assessed in clinical studies. Valproic acid coadministration did not affect the pharmacokinetics of MHD. MHD exposure was approximately 30-40% lower in patients who were coadministered carbamazepine (CBZ), phenobarbital (PB) and phenytoin (PHT). No dosage adjustment for Trileptal is recommended since the dose of OXC will be titrated in patients receiving CBZ, PB or PHT if their seizures are not controlled. The effect of OXC coadministration on antiepileptic drugs, CBZ, VPA and PHT was evaluated. The differences in the steady state exposure for CBZ, VPA and PHT in the presence of OXC and placebo were small and not statistically significant. These differences were an 8% increase, 8% decrease and 9% increase for steady state CBZ, VPA or PHT exposure,

respectively. These differences in CBZ, VPA and PHT exposures are probably not clinically significant.

Co-administration of Trileptal with an oral contraceptive has been shown to have an influence on the plasma levels of the two oral contraceptive components, ethinyl estradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE and LNG were decreased by [redacted] respectively. Therefore, concurrent use of Trileptal with hormonal contraceptives may render these contraceptives less effective. After repeated co-administration of Trileptal, the AUC values of felodipine were lowered by 28%. However the plasma levels remained in the recommended therapeutic range [redacted]. On the other hand, verapamil produced a decrease of 20% of the plasma levels of MHD. This decrease in plasma levels of MHD is not considered to be of clinical relevance. Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD, whereas viloxazine produced minor changes in MHD plasma levels (about 10% higher after repeated co-administration). Results with warfarin showed no evidence of interaction (no effect on prothrombin time) with either single or repeated doses of Trileptal.

## RECOMMENDATION

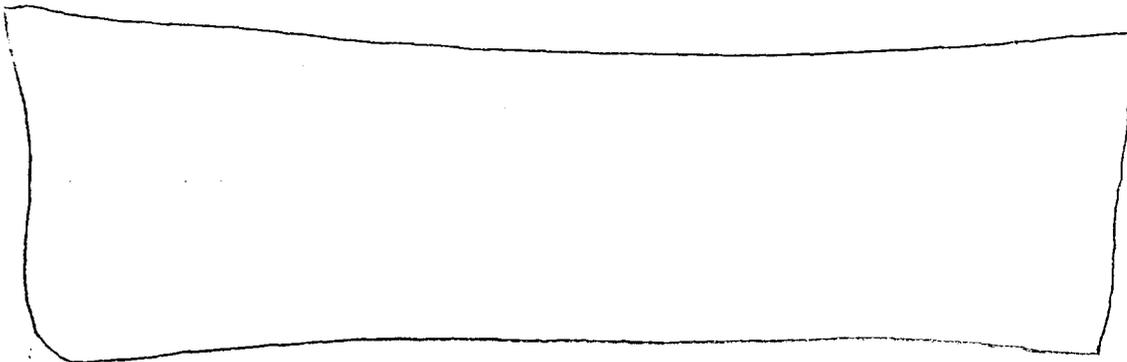
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I has reviewed NDA 21-014 (Oxcarbazepine (Trileptal™) submitted on September 25, 1998. The overall Human Pharmacokinetics Section is acceptable. This recommendation, comments (pages 33) and labeling comments (pages 33-34) should be sent to the applicant as appropriate.

## BACKGROUND

This review contains a summary of the studies submitted to the Human Pharmacokinetics and Bioavailability section in support of NDA 21-014. Individual study reports, including data, are on file in HFD-860 (Division of Pharmaceutical Evaluation I). The applicant is seeking approval of oxcarbazepine (Trileptal™) oral tablets (150, 300 and 600 mg tablets) in the USA.

Oxcarbazepine (OXC), the keto-analog of carbamazepine, is an orally active anticonvulsant that is presently registered in 47 countries. OXC is rapidly reduced by cytosolic enzymes to a monohydroxylated derivative (MHD) which is pharmacologically active. Formation of MHD is stereospecific with 2 enantiomers formed in the ratio of 80% (S-MHD) and 20% (R-MHD), both of which have similar activity. The anticonvulsant properties of OXC and MHD are possibly mediated by blocking voltage dependant sodium channels, decreasing high voltage activated calcium channels and interaction with potassium channels. The blockade of voltage dependant sodium channels in the brain has been proposed as the most plausible mechanism of action. This is based on results from: 1) in-vitro studies in which OXC and MHD limited sustained high frequency repetitive firing of sodium-dependant action potentials of cultured mouse neurons, and 2) in-vivo study (maximal electroshock) which evaluates the ability of drugs to prevent electrically induced tonic hind limb extension seizures in rodents. Efficacy in the maximal electroshock model has shown to correlate with the ability to prevent partial and generalized tonic-clonic seizures in humans; also drugs that are active in this test (e.g. carbamazepine, phenytoin) often interact with voltage dependant sodium channels. OXC is indicated as a first-line anticonvulsant drug for the treatment of partial seizures (simple, complex and partial seizures evolving to secondary generalized seizures) in adults and children. The drug is proposed for use as monotherapy or as adjunctive therapy.

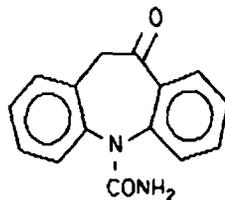
## BIOANALYTICAL METHODS TO MEASURE OXC AND MHD IN PLASMA



**BIOPHARMACEUTICS**

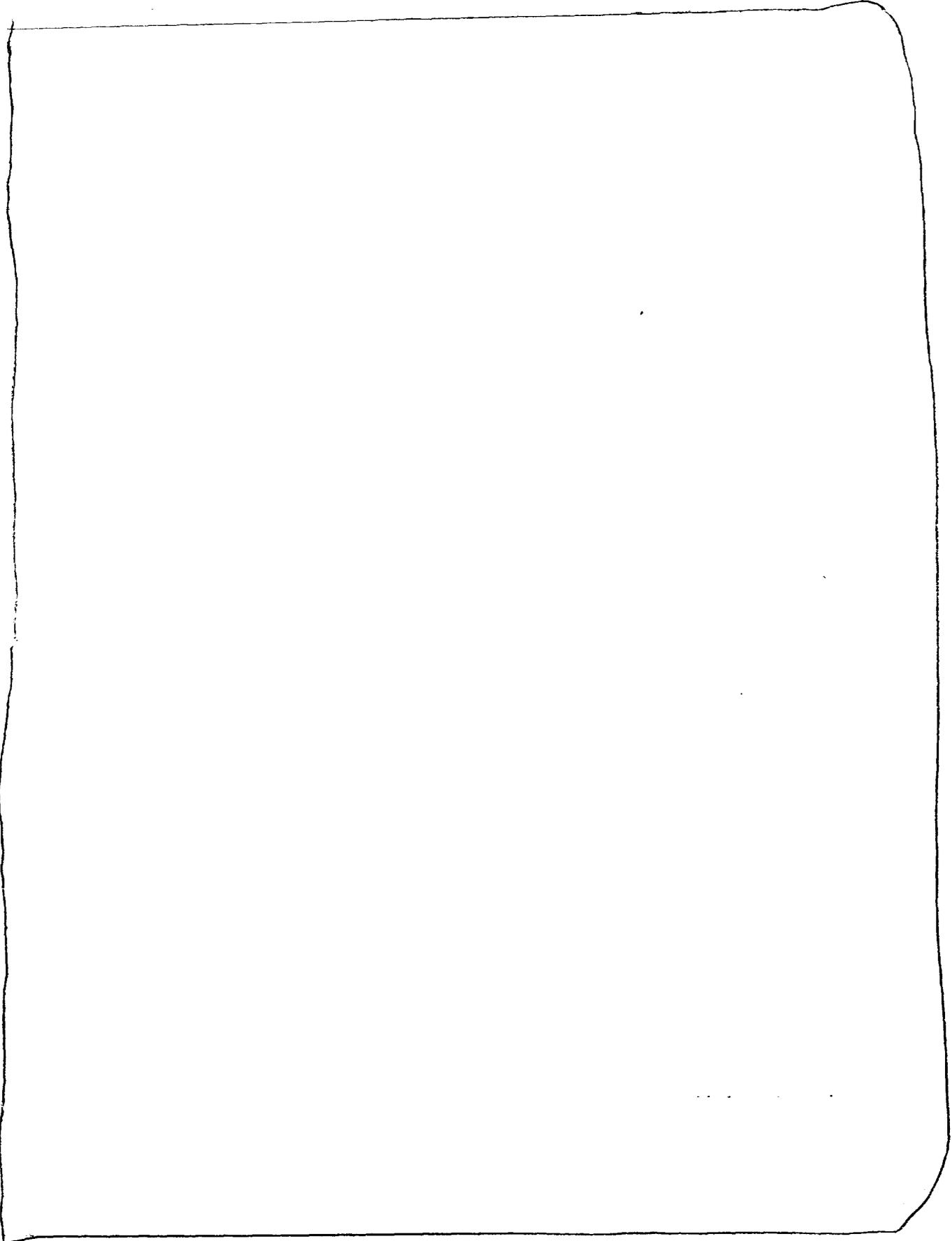
- Has the dosage form equivalence been established among different tablet strengths?
- Has the applicant developed an adequate dissolution method and specifications for quality control?
- What is the effect of food and how does it influence dosing recommendations?
- Are the clinical trial formulations (CTF), the pivotal trial formulations (PTF) and the current (European) market formulation (CMF) the same as the final market image (FMI)?

**CHEMISTRY:** The drug substance, OXC (10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide), is a tricyclic diarylazepine compound with anticonvulsant activity. OXC is a non-chiral, white to faintly orange crystalline powder with a molecular weight of 252.28. OXC has a  $pK_a$  of  $10.7 \pm 0.2$  and a partition coefficient of 1.31 (octanol/phosphate buffer pH 7.4, 25°C). It is slightly soluble in chloroform, dichloromethane, acetone and methanol and practically insoluble in ethanol, ether and water. No polymorphs of the solvent free drug substance have been observed.



Film-coated tablets were developed as the final dosage form of OXC to be marketed in the USA. The tablets are available in 3 strengths of 150 mg, 300 mg and 600 mg. The composition of all 3 dosage strengths is qualitatively identical and quantitatively proportional to the strength.

Ingredient (Core)	Function	Amount per unit (mg)			
		150 mg tablet	300 mg tablet	600 mg tablet	
OXC	Active	150.0	300	600	
	Glidant, Anticladherant				
	Disintegrant				
	Binder				
	Lubricant				
	Filler				
	Granulation fluid				
	Function				
	603	Film forming agent			
		Color pigment			
		Plasticizer			



appropriate for all 3 strengths of Trileptal. This recommendation will be conveyed to the applicant.

The multi-media in vitro dissolution profiles of the 150 mg and 300 mg FMI tablets were compared to the 600 mg FMI tablet using the similarity factor (F2). Since the 600 mg FMI tablet has been shown to be bioequivalent to the pivotal trial formulation (see below), it was used as the reference. The F2 values were calculated using the dissolution time points at 15, 30 and 60 minutes (drug release was > 85%). The results suggest that the dissolution profiles for the different tablet strengths are similar for all the four media tested (F2 > 50).

Similarity factor	Media	150 mg vs 600 mg	300 mg vs 600 mg
F-2 value	Water	64.00	90.44
F-2 value	0.1 M HCl	56.06	84.40
F-2 value	Acetate buffer pH 4.0	79.50	83.35
F-2 value	Phosphate buffer pH 6.8	67.07	66.79

**WAIVER OF BE STUDY FOR THE LOWER DOSAGE STRENGTH (150 and 300 MG OXC) OF THE FINAL MARKET IMAGE (FMI) FORMULATION:** The pivotal BE study was conducted using the highest strength of the final market image (FMI) formulation (see below). Following single and multiple doses, under fed conditions, the 600 mg FMI was found to be bioequivalent to the pivotal trial formulation (PTF) with respect to AUC and C<sub>max</sub>. The applicant's request for a waiver of the BE study for the two lower strengths of OXC (150 and 300 mg) based upon comparable multi-media dissolution profiles, compositional proportionality of the 3 strengths of OXC tablets and high permeability (F>95%) of the drug is acceptable.

**FOOD EFFECT:** The influence of food on the kinetics of OXC, MHD and DHD after a single, oral dose of 600 mg OXC in healthy volunteers was evaluated. Breakable tablets containing 600 mg of OXC were used. This formulation was the non-US current market formulation (F1) of Trileptal. This study utilized a single-center, randomized, open-label, 2 period, crossover design. Each subject received a single 600 mg dose of OXC in each of the treatments:  
Treatment A: 1 tablet of 600 mg OXC in fasted state, Treatment B: 1 tablet of 600 mg OXC following a high fat and high protein meal. The meal consisted of a total of approximately 870 kcal.

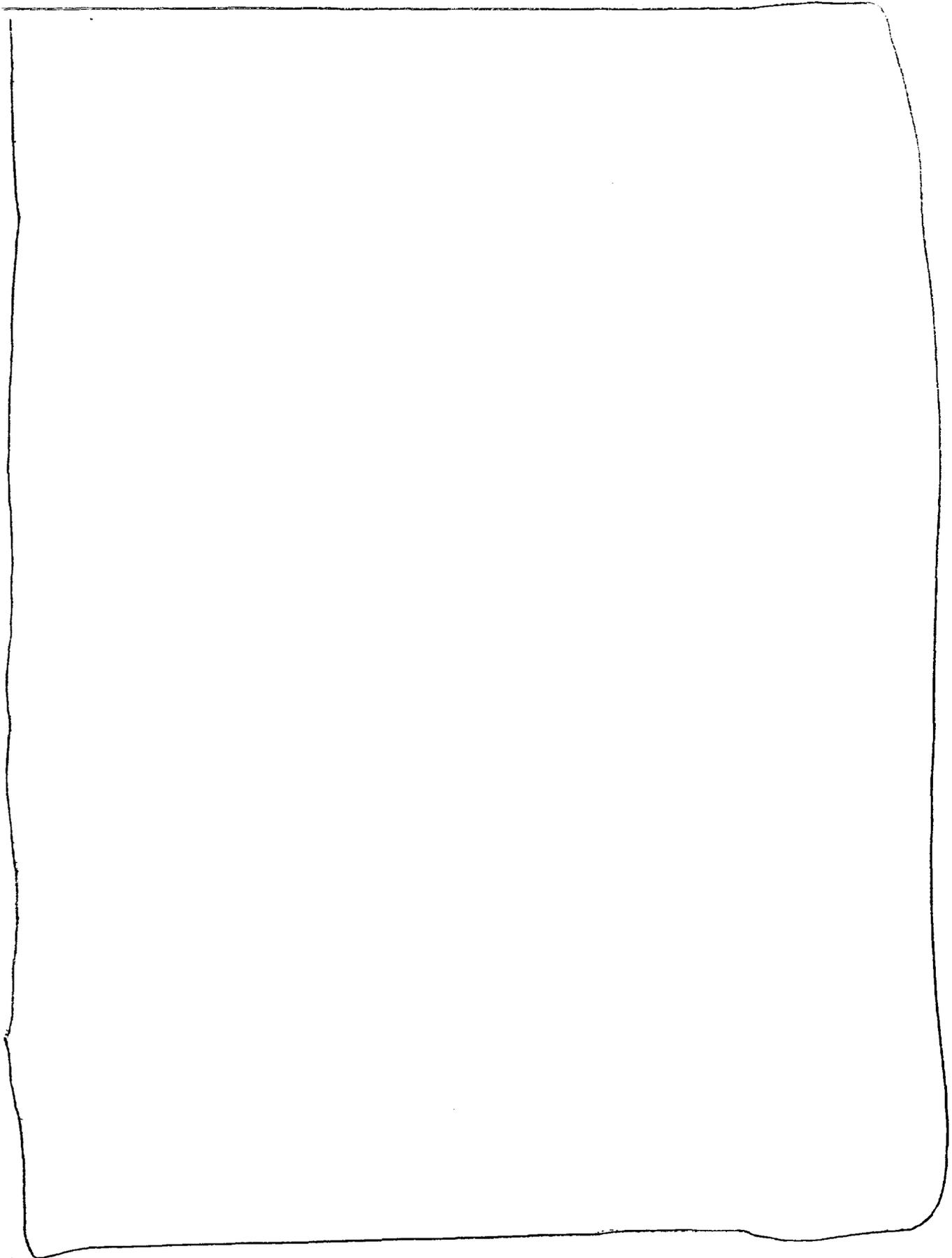
Mean (SD) Pharmacokinetic Parameters (n=6)

Compound	C <sub>max</sub> (nmol/g)		T <sub>max</sub> (h) as median		T <sub>1/2</sub> (hr)		AUC (nmol/g <sup>2</sup> h)	
	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
OXC	4.26 (1.44)	7.23 (4.79)	1	1.5	-	-	21.93 (4.48)	26.29 (6.59)
MHD	25.46 (4.84)	31.36 (5.26)	6	8	6.6 (1.7)	7.2 (1.3)	671.92 (86.81)	779.66 (88.03)
DHD	0.46 (0.13)	0.57 (0.09)	24	24	-	-	20.92 (5.24)	22.92 (4.16)

Relative bioavailability of fed vs fasted state (mean(SD); n=6)

Compound	AUC Ratio (Fed/Fasted)	AUC 90% CI	C <sub>max</sub> Ratio (Fed/Fasted)	C <sub>max</sub> 90% CI
OXC	1.19 (0.13)	(112%, 125%): PASS	1.60 (0.64)	114%, 199%): FAIL
MHD	1.17 (0.14)	(104%, 129%): FAIL	1.25 (0.18)	(109%, 141%): FAIL
DHD	1.16 (0.34)	(86%, 145%): FAIL	1.30 (0.23)	(110%, 150%): FAIL

Following administration of a high fat meal, administration of 600 mg OXC resulted in significant increases in AUC and C<sub>max</sub> values compared to the fasted state. For the main active moiety, MHD, coadministration with food resulted in an increase in AUC ranged from approximately 11%-39%; the C<sub>max</sub> was also increased significantly in the presence of food. The time to peak concentration was also increased from 6 hours in the fasted state to 8 hours in the presence of food. Both AUC and C<sub>max</sub> failed the bioequivalence (BE) criteria of 80%-125% when the parameters were compared in the fed and fasted states. The results from this study indicate that food affects the bioavailability of the current non-US market formulation of OXC (F1), resulting in



Treatment A: Trileptal 600 mg, formulation F1 (CMF); Batch number 013800

Treatment B: Trileptal 600 mg, formulation F4 (PTF); Batch number B970019

Treatment C: Trileptal 600 mg, formulation F5 (FMI in fed state); Batch number B97019

Treatment D: Trileptal 600 mg, formulation F5 (FMI in fasted state); Batch number B97019

The standardized high fat breakfast (on days 1 and 8 for fed subjects) consisted of 2 eggs fried in oil, 2 strips of bacon, 1 slice of toast with 10 g of butter, 2-4 oz hash brown potatoes and 240 ml full fat milk. The total energy content of the meal was approximately 997 kcal of which fat and protein comprised of 62% and 20% of the total calories, respectively.

The applicant has provided the following rationale for the study design used for this pivotal BE study. A multiple dose study was done since the pharmacokinetics of MHD are not predictable from single dose pharmacokinetics and in order to simulate conditions in the clinical situation. Also, the steady state pharmacokinetics of MHD have not been evaluated for the PTF and FMI. In this study, the CMF and the PTF have been administered under fed conditions (as opposed to the standard fasted condition). The applicant justifies this by stating that in a single dose (300 mg OXC) study, a significant food effect was observed with the CMF. A food effect study was not performed with the PTF or with the FMI earlier. The present recommendations (to patients as well as in clinical trials) involve taking the CMF and PTF with food, therefore the applicant has tested all the formulations under fed conditions. Also, in order to make clear recommendations regarding the effect of food on the FMI, this final formulation will be also tested under fasted conditions as part of the pivotal BE study.

**Mean (SD) PK Parameters for MHD following a Single 600 mg dose of OXC**

Treatment	N	AUC ( $\mu\text{mol}\cdot\text{h/l}$ )	$C_{\text{max}}$ ( $\mu\text{mol/l}$ )	$T_{\text{max}}$ (h) as median
CMF; fed	20	742 (110)	30.7 (4.6)	8
PTF; fed	20	768 (124)	34.7 (4.1)	6
FMI; fed	20	788 (128)	37.7 (4.5)	6
FMI; fasted	20	807 (126)	33.8 (5.5)	4.5

**Estimated ratio and 90% CI for the various comparisons following a SINGLE DOSE of 600 mg OXC**

Comparison	Ratio		90% CI	
	AUC	$C_{\text{max}}$	AUC	$C_{\text{max}}$
FMI vs PTF (fed conditions)	1.03	1.08	(99%-107%): PASS	(103%, 114%): PASS
FMI vs CMF (fed conditions)	1.06	1.23	(102%, 110%): PASS	(117%, 130%): FAIL
FMI (fed) vs FMI (fasted)	0.98	1.12	(94%, 102%): PASS	(106%, 118%): PASS

**Mean (SD) PK Parameters for MHD following multiple doses of 600 mg bid of OXC**

Treatment	N	AUC ( $\mu\text{mol}\cdot\text{h/l}$ )	$C_{\text{max}}$ ( $\mu\text{mol/l}$ )	$T_{\text{max}}$ (h) as median
CMF; fed	20	984 (140)	94.7 (14.1)	5.5
PTF; fed	20	982 (119)	96.7 (13.4)	6.5
FMI; fed	19	1000 (141)	99.4 (13.3)	5
FMI; fasted	20	1001 (181)	99.6 (12.0)	4

**Estimated ratio and 90% CI for the various comparisons following MULTIPLE DOSES of 600 mg bid of OXC**

Comparison	Ratio		90% CI	
	AUC 0-12	$C_{\text{max}}$	AUC 0-12	$C_{\text{max}}$
FMI vs PTF (fed conditions)	1.01	1.03	(98%-105%): PASS	(98%, 108%): PASS
FMI vs CMF (fed conditions)	1.01	1.05	(98%, 105%): PASS	(100%, 110%): PASS
FMI (fed) vs FMI (fasted)	0.99	1.00	(96%, 103%): PASS	(85%, 104%): PASS

Following single and multiple doses of 600 mg dose of OXC under fed conditions, FMI film coated formulation was bioequivalent to the PTF film coated formulation. Food had no effect on the bioavailability of the FMI following single and multiple doses of 600 mg dose of OXC. Comparison of the FMI (film coated final market image) to the CMF (uncoated current market formulation) under single dose, fed conditions showed that the FMI was not bioequivalent to the CMF. The FMI failed the bioequivalence criteria for  $C_{\text{max}}$  when compared with the CMF (90% CI=117%, 130%), indicating that the peak concentrations of MHD achieved following the FMI were significantly higher than those following administration of the CMF.

## CLINICAL PHARMACOLOGY

### IN-VITRO DISTRIBUTION STUDIES

**Protein binding:** At therapeutic concentrations, OXC was moderately bound to serum proteins (76%), whereas binding of MHD was low (40%). The free fraction of both compounds, OXC and MHD increased at higher concentrations (MHD: 40.4% bound at 10  $\mu\text{g/ml}$  and 28.6% bound at 100  $\mu\text{g/ml}$ ; OXC 68% bound at 10  $\mu\text{g/ml}$  and 58.5% bound at 20  $\mu\text{g/ml}$ ). The protein binding of OXC was slightly influenced by MHD, the binding of MHD was not affected by OXC. The inter-subject variability was low for both OXC and MHD. Albumin was the major protein responsible for binding to serum proteins for OXC and MHD. Binding of OXC and MHD to gamma globulin and AAG was negligible. The binding of OXC and MHD to erythrocytes was constant up to concentrations of 20 and 25  $\mu\text{g/ml}$  of OXC and MHD, respectively. The concentrations of OXC and MHD were higher in erythrocytes than in plasma (erythrocyte-to-plasma ratio = 1.8 and 1.9 for MHD and OXC, respectively).

**MASS BALANCE:** A single dose study in two healthy volunteers using 400 mg [14-C]OXC were done to characterize the routes of excretion and metabolism of OXC. Two healthy males received a single oral 400 mg dose of [14-C]OXC, as solid substance in a gelatin capsule. The total administered radioactivity was 96.4  $\mu\text{Ci}$  in each volunteer. Blood samples were collected prior to dosing, and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 168 hours post dose. Urine and feces were collected at 24-hour intervals for up to 10 days.

Within the first day after dosing, approximately 57% of the dose was recovered in urine and feces (predominantly in urine). Elimination was essentially complete at 6 days post-dose. In both volunteers, most of the dose (over 94%) was renally excreted and less than 5% was excreted in the feces. This suggests that OXC is almost completely absorbed from the gastrointestinal tract. Maximum plasma concentrations of total radioactivity were reached 4 hours post-dose. Only low (approximately 2%) concentrations of OXC were present in plasma. OXC was rapidly converted to a high extent to the monohydroxy (MHD) metabolite. MHD accounted for over 65% of the total AUC in both subjects. The second metabolite CGP 10000 (trans dihydroxy derivative) was also present in low concentrations in plasma. Plasma concentrations of OXC were below 0.01  $\mu\text{g/ml}$  48 hours post-dose whereas MHD was still present in considerable amounts (0.5  $\mu\text{g/ml}$ ).

Characterization of the excretion products in urine showed that the most prominent metabolite in urine was MHD which accounted for 49% and 61% of the total urinary radioactivity in each subject. OXC was present in small amounts in urine (7.7% and 10.9%, respectively in each subject). CGP 10000 was also present in small amounts in urine (6.7% and 2.3%, respectively in each subject). Therefore, 3 compounds, intact OXC, MHD, and the trans dihydroxy derivative were recovered in urine of both volunteers; these accounted for 63.6% and 74.1% of the total radioactivity, respectively.

### PHARMACOKINETICS (PK)

- What is the pharmacokinetic behavior of OXC in healthy subjects and in epileptic patients?
- Are the pharmacokinetics in epileptic patients similar to those in healthy volunteers?
- Are the pharmacokinetics different between males and females (effect of gender)?
- Are the pharmacokinetics different between young adults and the elderly? (effect of age)?

**SINGLE DOSE PHARMACOKINETICS IN HEALTHY VOLUNTEERS (YOUNG AND ELDERLY)**

**A dose dependency, crossover (3-week washout) study of the bioavailability following OXC in man (3 males, 3 females) after single, oral doses of 150, 300 and 600 mg of OXC:**

**Mean (SD) Pharmacokinetic Parameters for MHD in Healthy Young Subjects Following Single Oral Doses Of 150 mg, 300 mg and 600 mg OXC (N=6)**

PK Parameters	Dose (mg)		
	150 mg	300 mg	600 mg
$C_{max}$ ( $\mu\text{g/g}$ )	1.90 (0.28)	3.30 (0.88)	5.98 (2.06)
$T_{max}$ (h)	Median =4	Median =4	Median =4
AUC ( $\mu\text{g}\cdot\text{h/g}$ )	35.73 (8.58)	83.32 (36.46)	179.27 (38.97)

The mean AUC's for OXC in plasma reached approximately 1 to 2% of the administered doses. Due to the low concentrations of OXC in plasma, the applicant has assessed dose-dependency on the basis of the plasma concentrations of MHD.  $C_{max}$  and AUC for MHD appear to be related to dose; the increase in AUC with respect to dose is slightly more than dose-proportional.

The tolerability and pharmacokinetics MHD and its enantiomers was evaluated after a single intravenous dose given as a racemate. A pilot study was first performed in 3 healthy males in which intravenous doses of MHD used were 150, 200 and 250 mg (one subject per dose level). Preliminary pharmacokinetic data from the pilot study indicated that MHD exposure increased with dose. The 250 mg dose was selected for the next study since it was well tolerated. This study was a 2-way crossover study in 12 healthy males and females. Subjects received a single IV dose of 250 mg MHD. Intravenous MHD was infused over 30 minutes.

**Mean (SD) Pharmacokinetic Parameters following intravenous administration of 250 mg MHD (n=12)**

PK Parameters	MHD	OXC	DHD	R-MHD	S-MHD
$C_{max}$ ( $\mu\text{mol/L}$ )	N/a	0.08 (0.13)	0.24 (0.20)	N/a	N/a
$T_{max}$ (h)	N/a	0.5	8.0	N/a	N/a
AUC ( $\mu\text{mol}\cdot\text{hr/L}$ )	261.9 (51.0)	0.47 (0.78)	7.5 (7.25)	119.5 (25.9)	166.8 (36.5)
$T_{1/2}$ (h)	8.7 (1.9)	N/a	N/a	9.0 (1.5)	10.6 (2.6)

In plasma, following a 30 min intravenous (iv) infusion of MHD, the oxidized metabolite OXC accounts for 0.2%, and DHD accounted for 2.6% of the overall AUC for MHD. The two enantiomers of MHD were the major components detected in plasma following iv MHD. The ratio of AUC for the two enantiomers shows a predominance of the S- compared to the R- (S to R ratio = 1.4). The mean terminal half lives were similar for the 2 enantiomers.

Approximately 16% and 12% of the S- and R- enantiomers were excreted unchanged in urine. MHD undergoes extensive metabolism by glucuronidation (O-glucuronidation); approximately 45% of the dose was excreted in urine as glucuronide conjugates. The glucuronide of S-MHD was present to a greater extent than that of R-MHD. OXC was scarcely excreted in urine and DHD was renally excreted to a minor extent (3.9% of the dose).

The tolerability and pharmacokinetics of MHD and its enantiomers was evaluated after an oral dose of OXC. Following oral administration of 300 mg OXC to 12 healthy males and females in the fasted state, the major metabolite in plasma was MHD; only low amounts of OXC and DHD were detected in plasma (2.2% and 1.8%, respectively). The AUC ratio of the S- to the R- enantiomer was approximately 4.0; S-MHD was the predominant enantiomer in plasma following oral OXC. The mean terminal  $t_{1/2}$  for the S- and the R- enantiomer was approximately 11 hours and 16 hours, respectively. The difference in the half-life between the 2 enantiomers may be due to the difference in the rate of metabolism.

**Mean (SD) Plasma Pharmacokinetic Parameters following oral administration of 300 mg OXC (n=12)**

PK Parameters	MHD	OXC	DHD	R-MHD	S-MHD
$C_{max}$ ( $\mu\text{mol/L}$ )	N/a	2.0 (0.7)	0.2 (0.2)	3.0 (0.81)	11.0 (2.2)
$T_{max}$ (h)	N/a	1.0	24.0	3.5	4.0
AUC ( $\mu\text{mol}\cdot\text{hr/L}$ )	308 (66.7)	6.8 (1.9)	5.4 (7.3)	63.9 (19.5)	241.4 (54.8)
$T_{1/2}$ (h)	11.4 (3.3)	N/a	N/a	15.8 (2.8)	11.2 (1.5)

Following oral administration of OXC, the major metabolite excreted in urine were the glucuronide conjugates of S- and R-MHD; approximately 44% of the oral dose was excreted in urine as glucuronide conjugates. The glucuronide of S-MHD was present to a greater extent than that of R-MHD. Unchanged MHD was also renally excreted (27%); OXC was scarcely excreted in urine and DHD was renally excreted to a minor extent (2.7% of the dose).

A single dose pharmacokinetic study of OXC in 12 healthy young female volunteers was conducted. The objectives of the trial were to determine the pharmacokinetics of MHD after a single dose of 600 mg OXC in healthy young females. Doses were given after an overnight fast.

Mean (SD) Pharmacokinetic Parameters for MHD Following A Single 600 Mg Dose Of (N=12)

PK Parameters	Single dose
C <sub>max</sub> (µg/mL)	5.17 (0.98)
T <sub>max</sub> (h)	Median = 4.1
T <sub>1/2</sub> (h)	16.1 (3.9)
AUC <sub>inf</sub>	135.4 (30.5)
AUCT	N/a
Amt. excreted in urine (0-96 h) (mg)	169.3 (45.2)
Amt. excreted in urine (240-252 h) (mg)	N/a

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The PK parameters for MHD obtained in young females were similar to those obtained in an earlier single dose study in healthy males and females.

A single dose pharmacokinetic study of OXC in 12 healthy elderly female volunteers was conducted. The objectives of the trial were to determine the pharmacokinetics of MHD after a single dose of 600 mg OXC in healthy elderly females. Doses were given after an overnight fast.

Mean (SD) Pharmacokinetic Parameters for MHD Following A Single 600 Mg Dose Of OXC (N=12)

PK Parameters	Single dose
C <sub>max</sub> (µg/mL)	7.20 (1.58)
T <sub>max</sub> (h)	Median = 5.9
T <sub>1/2</sub> (h)	24.2 (13.8)
AUC <sub>inf</sub>	221.6 (40.6)
AUCT	N/a
Amt. excreted in urine (0-96 h) (mg)	172.6 (33.3)
Amt. excreted in urine (240-252 h) (mg)	N/a

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The pharmacokinetic data for MHD in elderly females was compared to the data obtained from a study in young healthy volunteers given the same dose of OXC. The C<sub>max</sub> and AUC for MHD appear to be higher and t<sub>1/2</sub> for MHD seems to be longer in elderly females compared to young subjects after a single 600 mg dose of OXC.

A single dose pharmacokinetic study of OXC in healthy young and elderly male volunteers was conducted. The study was open label; OXC was administered as a single 300 mg dose. Doses were administered after an overnight fast.

Mean (SD) Pharmacokinetic Parameters for MHD in Healthy Males Following A Single 300 Mg Dose Of OXC (N=12)

PK Parameters	Single Dose (Elderly)	Single dose (Young)
C <sub>max</sub> (µg/mL)	2.88 (0.33)	2.33 (0.38)
T <sub>max</sub> (h)	Median=5	Median=4
T <sub>1/2</sub> (h)	19.3 (4.1)	13.9 (3.3)
AUC <sub>inf</sub>	85.0 (14.4)	56.1 (13.7)

Statistical analysis comparing the pharmacokinetic parameters for MHD between the young and the elderly males indicated that the exposure and peak concentrations of MHD were significantly higher in the elderly compared to young volunteers, after a single dose of OXC. The elimination rate constant was also significantly different (smaller) in the elderly, resulting in a longer terminal half-life compared to that in young subjects. The applicant has related average K<sub>el</sub> in each subject to the corresponding creatinine clearance (for young and elderly). The resulting graph suggests a

positive correlation when all subjects were used in the regression analysis. However, within either age group, there was no significant correlation between  $K_{el}$  and creatinine clearance. The higher peak concentrations and exposure and the lower  $K_{el}$  in the elderly subjects suggests a lower clearance of MHD in this age group. Since MHD is mainly glucuronidated and excreted in the urine, the differences observed may be due the difference in creatinine clearance (renal function) between the elderly and the young subjects. In a clinical situation, a low dose of OXC will be administered (600 mg/day) after which the dose is adjusted individually until a therapeutically effective maintenance dose is reached. Because of individual dose-titration of OXC in epileptic patients, the age-related differences in the pharmacokinetics of MHD probably do not have clinical implications, but a lower starting dose may be recommended.

#### MULTIPLE DOSE PHARMACOKINETICS IN HEALTHY VOLUNTEERS (YOUNG AND ELDERLY)

Steady-state plasma concentration-time profiles of OXC, MHD and DHD were obtained in healthy volunteers after repeated 600 and 1200 mg doses of OXC. The study was a sequential design trial. Eight subjects (4 males and 4 females) received multiple doses of a total of 600 mg OXC per day in the first study period, followed by multiple doses of a total of 1200 mg OXC per day in the second period. There was a washout period of 3 weeks between each period. Trt 1: Daily dose of 600 mg OXC given as: 300 mg bid (4 subjects) and 150 mg qid (4 subjects) for 3 weeks, followed by, Trt 2: Daily dose of 1200 mg OXC given as: 600 mg bid (4 subjects) and 300 mg qid (4 subjects) for 3 weeks.

Mean (SD) Pharmacokinetic Parameters for MHD in Healthy Young Subjects Following Multiple Daily Doses Of 600 mg and 1200 mg OXC (N=8)

PK Parameter	600 mg OXC			1200 mg OXC		
	MHD	OXC	DHD	MHD	OXC	DHD
$C_{max}$ ( $\mu\text{mol/l}$ )	34.4 (6.6)	1.8 (1.0)	1.9 (0.8)	72.3 (9.1)	3.8 (2.2)	4.4 (1.3)
$T_{max}$ (h)	6	2	7	3	2	3
AUC <sub>0-24</sub> ( $\mu\text{mol}\cdot\text{h}$ )	341.4 (6.6)	9.6 (4.6)	17.6 (8.3)	746.3 (98.8)	20.9 (9.8)	47.2 (14.2)

The AUC values of MHD for the bid versus the qid regimens were not significantly different; therefore the values were averaged to obtain the mean parameters for each dose. Mean AUC and  $C_{max}$  for all 3 compounds increased in relation to dose. The plasma concentrations of OXC and DHD observed for the 600 mg dose of OXC were close to the limit of quantitation of the analytical method. Therefore, the pharmacokinetic parameters calculated for OXC and DHD may be less accurate. Statistical comparison of the dose-corrected pharmacokinetic parameters for MHD showed no differences, suggesting a linear and dose proportional increase of AUC and  $C_{max}$  under steady state conditions.

A multiple dose pharmacokinetic study of 300 mg bid OXC in 12 healthy young female volunteers was conducted. Doses were administered after an overnight fast.

Mean (SD) Pharmacokinetic Parameters for MHD Following Multiple Doses (150 Mg Bid For One Day Followed By 300 Mg Bid For 4.5 Days (N=12))

PK Parameters	Multiple dose
$C_{max}$ ( $\mu\text{g/ml}$ )	9.34 (1.06);
$T_{max}$ (h)	Median = 3.0;
$T_{1/2}$ (h)	14.2 (2.6);
AUC	91.5 (11.8);
AmL Excreted in urine (240-252 h) (mg)	122.0 (15.4);

The inter-individual variability in the pharmacokinetic parameters for MHD was relatively small. Comparison to results from the single dose component of this study (see above) was done. The results on  $C_{max}$  (after correcting for dose) indicated that there was approximately 3-4 fold accumulation of MHD following multiple dosing. Statistical analysis indicated that  $T_{max}$  occurred slightly earlier following multiple doses compared to  $T_{max}$  following a single dose. The

elimination half-life of MHD was similar following single and multiple doses of OXC. The dose corrected AUCT following multiple doses is larger than AUCinf following a single dose, suggesting that accumulation is greater than that expected for a drug exhibiting dose-proportional pharmacokinetics. A similar pattern was observed for the amount of MHD excreted in urine. The % of OXC dose recovered in urine as MHD ranged from [redacted] (mean = 45%).

**A multiple dose pharmacokinetic study of 300 mg bid OXC in 12 healthy elderly female volunteers was conducted. Doses were administered after an overnight fast.**

Mean (SD) Pharmacokinetic Parameters for MHD Following Multiple Doses (150 Mg Bid For One Day Followed By 300 Mg Bid For 4.5 Days in Healthy, Elderly Females (N=12))

PK Parameters	Multiple dose
$C_{max}$ ( $\mu\text{g/mL}$ )	11.72 (1.97)
$T_{max}$ (h)	Median = 3.0
$T_{1/2}$ (h)	16.5 (2.8)
AUCT	121.9 (20.2)
Amt. excreted in urine (240-252 h) (mg)	115.8 (19.0)

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The inter-individual variability in the pharmacokinetic parameters for MHD was relatively small. Comparison to results from the single dose component of this study (see previous page) was done. The results on  $C_{max}$  (after correcting for dose) indicate that there was a greater than 3-fold accumulation of MHD following multiple dosing. Statistical analysis indicated that  $T_{max}$  occurred earlier following multiple doses compared to  $T_{max}$  following a single dose. The elimination half-life of MHD following multiple doses of OXC was shorter than that following a single dose, suggesting that some induction of the elimination process may occur during multiple dosing. The dose corrected AUCT following multiple doses was slightly larger than AUCinf following a single dose, suggesting that accumulation is greater than that expected for a drug exhibiting dose-proportional pharmacokinetics. A similar pattern was observed for the amount of MHD excreted in urine. The % of OXC dose recovered in urine as MHD ranged from [redacted] (mean = 43%).

The pharmacokinetic data for MHD in elderly females was compared to the data obtained from a study in young healthy volunteers given the same dose(s) of OXC. The  $C_{max}$  and AUC appear to be higher (23% and 33%, respectively) and  $t_{1/2}$  for MHD seems to be longer (15%) in elderly females compared to young subjects, after multiple dosing.

**A multiple dose (300 mg bid of OXC) pharmacokinetic study of Trileptal in healthy young and elderly male volunteers was conducted. Doses were administered after an overnight fast.**

Mean (SD) Pharmacokinetic Parameters for MHD in Healthy Males Following Multiple Doses (300 Mg Bid For 7.5 Days (N=12))

PK Parameters	Multiple dose (Elderly)	Multiple dose (Young)
$C_{max}$ ( $\mu\text{g/mL}$ )	12.03 (1.21)	8.49 (1.98)
$T_{max}$ (h)	Median=4	Median=2
$T_{1/2}$ (h)	26.5 (6.7)	14.2 (3.4)
AUCT	132.7 (14.9)	86.8 (19.0)

Statistical analysis comparing the pharmacokinetic parameters for MHD between the young and the elderly males indicated that the exposure and peak concentrations of MHD were significantly higher (approx 50%, in each case) in the elderly compared to young volunteers, after multiple doses of OXC. The elimination rate constant was also significantly different (smaller) in the elderly, resulting in a longer terminal half-life (almost 2-fold greater) compared to that in young subjects. The applicant has related average  $K_{el}$  in each subject to the corresponding creatinine clearance (for young and elderly). The resulting graph suggests a positive correlation when all subjects were used in the regression analysis. However, within either age group, there was no significant correlation between  $K_{el}$  and creatinine clearance. The higher peak concentrations and exposure and the lower  $K_{el}$  in the elderly subjects suggests a lower clearance of MHD in this age group. Since MHD is mainly glucuronidated and excreted in the urine, the differences observed may be due the difference in creatinine clearance (renal function) between the elderly and the

young subjects. In the clinical situation, a low dose of OXC is administered after which the dose is adjusted individually until a therapeutically effective maintenance dose is reached. Because of individual dose-titration of OXC in epileptic patients, the age-related differences in the pharmacokinetics of MHD probably do not have clinical implications. However a lower starting dose may be recommended in the elderly patients.

**MULTIPLE DOSE PHARMACOKINETICS IN EPILEPTIC PATIENTS (see section below)**

**DOSE-RESPONSE AND PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) RELATIONSHIPS**

**A dose-response study of the effects of OXC on memory and psychomotor functions in normal volunteers was conducted. The study was designed to assess the effects of repeated administration of OXC on memory and psychomotor performance compared to placebo using 2 dose levels of OXC (150 and 300 mg bid). The study was a double blind, balanced, crossover comparison of two dose levels of OXC with placebo in 12 healthy adults (5 males and 7 females). Each volunteer received the following treatments according to a balanced randomization schedule: A=150 mg OXC qd for days 1-7 followed by 150 mg bid for days 8-15, B=300 mg OXC qd for days 1-7 followed by 300 mg bid for days 8-15, C=placebo qd for days 1-7 followed by placebo for days 8-15. There was a washout period of at least 3 weeks between study periods.**

Pharmacodynamic endpoints were measured at 0 hr and 4 hr post-dose on Days 1, 8 and 15: Electroencephalogram (EEG): EEG activity in the 4 bands of the power spectrum (Theta, Delta, Alpha and Beta) were obtained from recordings made from 2 electrodes, Cz and C3, Assessment of working memory was done using several tests including visual working memory, the Baddeley Logic Test, Digit Span, free recall test, news recall and word fluency, Psychomotor assessments were made using several tests including finger tapping, digit cancellation and digit-symbol-substitution-task. Subjective ratings were evaluated using 16 self rated visual analog scales and bodily symptoms were rated using another set of self rated visual analog scales.

Statistical analysis was done using a repeated measures multivariate analysis of variance using the GLM procedure in SAS. The inter-individual variability for treatment and period effects was evaluated, as well as the intra-individual variability in terms of effects of day (1, 8, and 15) and time (pre- and post-drug). Statistical analysis indicated that for the EEG, in the eyes open condition, there were significant treatment differences in theta and beta activity, such that a greater activity was effected by a higher dose of OXC. Assessment of the results on memory tasks showed that they were not affected by study treatment. Performance on the psychomotor tests indicated no significant treatment effects for majority of the tests. Performance on the symbol copying and cancellation tasks was enhanced on OXC compared to placebo. Subjective mood ratings showed significant treatment effects; the 150 mg dose of OXC showed increased feelings alertness, clearheadedness and quickwittedness (pooled together as Mood Factor 1) compared to placebo. Bodily symptoms of palpitations and shaking showed significant treatment effects with the 300 mg dose of OXC showing increased feelings of palpitation and shaking compared to placebo.

In an attempt to identify any association between pharmacodynamic effects and plasma concentrations of MHD, the relationship between plasma trough MHD concentrations and pharmacodynamic effects (which were statistically significant) were evaluated by the reviewer. Overall, there did not appear to be a relationship between plasma trough MHD concentrations and pharmacodynamic effects of OXC in this study. In general, results from this study indicated that the doses of OXC used in healthy volunteers produced little psychomotor/cognitive changes.

**A double blind, within-subject study was conducted to compare the effect of cognitive functions of OXC, with those of phenobarbitone (PB) and placebo after single oral doses to healthy volunteers. The study was designed to assess the effects of a single oral dose of**

OXC 600 mg (2x300 mg) in comparison with PB 66 mg and placebo on cognitive function. The study was a double blind, 3-period, crossover comparison of OXC with PB and placebo in 22 healthy adult (12 males and 10 females) volunteers. There was a washout period of 9 days between study periods. Volunteers were administered study medication following a breakfast meal. The following pharmacodynamic endpoints were measured predose (0 hr) and 2, 4, 7, and 24 hours post-dose: Simple reaction time test, binary reaction time test, finger tapping test, computerized visual searching test, recognition test.

Statistical analysis was done to compare OXC and PB for treatment differences and PB versus placebo to test the sensitivity of the trial. Confirmatory analysis was performed for the reaction time tests and recognition task using an analysis of covariance appropriate for a 3-period crossover study. The baseline of each treatment period was used as a covariate in the analysis. As part of exploratory analyses, a summary measure (AUC0-24) was obtained for the simple reaction test and recognition task and these values were analyzed using an analysis of variance appropriate for a 3-period crossover study. Statistical analysis showed no significant differences between the 3 treatments in any of the primary measures for the pharmacodynamic tests. No clinically relevant differences in cognitive function were observed in healthy volunteers following single doses of 600 mg OXC, 66 mg PB or placebo. This may be due to the low doses of test drugs used in the study, the single dose nature of the study or to the poor sensitivity of the test battery in healthy volunteers.

A multicenter, randomized, double blind, placebo-controlled, parallel, add-on trial of oxcarbazepine (OXC) was conducted to evaluate the safety and efficacy of OXC, as adjunctive therapy, relative to placebo in children (4-17 years) with inadequately controlled partial seizures. A secondary objective of this trial was to explore the pharmacokinetic-pharmacodynamic (efficacy and safety) relationships of OXC in the pediatric population, as well as explore the drug-drug interaction potential of OXC when given with other antiepileptic drugs (AEDs). The study design allowed patients with inadequate seizure control to continue on a stable regimen of one or two AEDs, in addition to receiving OXC or placebo. The trial consisted of 3 phases:

Phase Period	Baseline		Double Blind Phase					
			Titration		Maintenance			
Visit	1	2	3	4	5	6	7	8
Day	-56 to -1	0	14	28	42	56	84	112
Treatment	1 - 2 AEDs		OXC or Placebo plus 1 - 2 AEDs					
↑ randomization								

Titration period for OXC/placebo began between Visit 2 and 3 and lasted for 14 days. This was followed by a 98 day maintenance period. The 14-day titration schedule is shown below.

Days	Dose (mg/kg/day, P.O.)
1 - 2	10
3 - 6	20
7 - 10	30
11 - 14	Randomized dose or max. tolerated dose (whichever was less)

Based on the body weights recorded at Visit 2, the patients' target randomized trial drug doses were determined on a mg/kg basis, based on weight categories:

Body weight on Visit 2	Target randomized Daily Dose
20 - 29.0 kg	900 mg (31 mg/kg to 45 mg/kg)
29.1 - 39.0 kg	1200 mg (31 mg/kg to 41 mg/kg)
39.1 - 60.0 kg	1800 mg (30 mg/kg to 46 mg/kg)
Body weights of greater than 60 kg were randomized to the 1800 mg dose.	

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At selected sites, blood samples were collected prior to the morning dose at Visits 5-8, or when a patient terminated the trial for the determination of trough plasma concentrations of the OXC metabolites, MHD and DHD. Patients were required to record the time of their last 3 doses prior to the visit. Non linear mixed effects models were fitted to the plasma concentrations of MHD using NONMEM Version 4. A one compartment model with first order input and first order output was used. This pharmacokinetic model consisted of 4 parameters: apparent clearance (Theta1), volume of distribution (Theta2), absorption rate constant (Theta3), and absorption time-lag constant (Theta4). Model building strategies were employed in stages. Stage 0 identified the residual error model, Stage 1 identified the random effects and their covariance structure, Stage 2 selected the best 2 covariates (excluding AEDs) followed by inclusion of any 7 AEDs. The AEDs were: carbamazepine (CBZ), diazepam, gabapentin, lamotrigine, phenobarbital, phenytoin and valproic acid.

From the final model, the minimum steady state concentrations (Cmin) were estimated for each patient using an average dose from Visits 3-8 given every 12 hours. Cmin was used to explore possible relationships between MHD pharmacokinetics and the primary efficacy variable - % change in seizure frequency of the double blind treatment phase from the baseline phase, using a regression model. In addition relationship(s) of Cavg (average steady-state plasma concentration), Cmax (maximum concentration at steady-state and Cl/F (apparent clearance) to the primary efficacy variable was explored.

For the concomitant AEDs (listed above), plasma drug concentrations were measured at baseline as well during the double blind phase. The patient's average of the AED concentration at baseline and during treatment was computed for each AED, and a ratio (treatment/baseline) was calculated. The relationship between Cmin and the AED levels relative to baseline was explored.

To explore pharmacokinetic-efficacy relationships, Cmin was used as an explanatory variable in regression models for the primary outcome - % change in seizure frequency of the double blind treatment phase from the baseline phase. The models fitted to the data were of the form:

$Y = \beta_0 + \beta_1 \text{Seiz}_{\text{baseline-28}} + \beta_2 \text{TRT} + \beta_3 \text{Cmin}$ ; where  $Y = 100\%(\text{Seiz}_{28} - \text{Seiz}_{\text{baseline-28}} / \text{Seiz}_{28})$  or percentage change in seizure frequency.  $\text{Seiz}_{28}$  and  $\text{Seiz}_{\text{baseline-28}}$  are the 28-day double blind and baseline seizure frequencies, respectively, TRT is the treatment group (placebo=0 or OXC=1) and  $\beta_0, \beta_1, \beta_2, \beta_3$  are regression parameters.

Safety outcomes for which relationships with plasma concentrations were explored included adverse events (AEs) and abnormalities in clinical laboratory assessments. The AEs that were included were ataxia, diplopia, dizziness, headache, nausea, somnolence and vomiting. The clinical laboratory variable that were included were alkaline phosphatase, SGOT, SGPT, sodium and WBCs. Relationships between Cmin and the AEs (and clinical labs) were explored.

Pharmacokinetic analysis was performed only for MHD, the active metabolite of OXC. The final population pharmacokinetic model contained a combined residual error model and two random effects: Cl/F and V/F. Body surface area and three AEDs (CBZ, phenobarbital and phenytoin) were the covariates affecting Cl/F. Height was the covariate affecting V/F. The addition of other covariates (e.g. age, race, gender) to the final model were not significant. The population estimate for Cl/F in children (with BSA of  $1.3 \text{ m}^2$ ) was 2.33 L/h. Based on this trial in children, the Cl/F for a typical adult with a BSA of  $1.8 \text{ m}^2$  was estimated to be 3.1 L/h. This extrapolation to adults is consistent with results from monotherapy trials with OXC in adults where apparent clearance for a typical adult was 3 L/h. Estimated Cl/F for MHD with coadministration of CBZ, phenobarbital or phenytoin were 31-35% higher than with no coadministration. This is consistent with an earlier in-vivo drug interaction study, where phenobarbital, CBZ and phenytoin have been shown to decrease the steady state plasma concentrations of MHD by 30-40%. The magnitude of the effect of MHD on other AEDs was small (approximately 15%) and probably not clinically significant.

The primary efficacy variable, % change in 28-day seizure frequency relative to baseline was fit to a regression model. The % change in 28-day seizure frequency relative to baseline was significantly related to treatment group or  $C_{min}$  ( $p < 0.001$  for each), using baseline seizure frequency as a covariate. However, R-squared and root mean square error were not significantly different for the different pharmacokinetic-efficacy models.

Relationships between  $C_{min}$  and the AEs (and clinical labs) were explored. Based on statistical significance, patients with higher  $C_{min}$  were associated with higher incidences than the patients on placebo for ataxia, diplopia, dizziness, headache, nausea, somnolence and vomiting (however, scatter plots do not suggest a clear relationship between  $C_{min}$  and the incidence of any of the observed AEs).

The safety and efficacy of 1200 mg/day of OXC was conducted to evaluate the safety and efficacy of OXC monotherapy relative to placebo in untreated patients with recent onset partial seizures. A secondary objective of this trial was to explore the pharmacokinetic-pharmacodynamic (efficacy and safety) relationships in OXC monotherapy. The study was a multicenter, double blind, randomized, placebo controlled, parallel group trial to investigate the safety and efficacy of OXC monotherapy (1200 mg/day) compared to placebo in patients (10 years or older) who were not receiving antiepileptic drug (AED) therapy for partial seizures.

Phase	Baseline		Double Blind Phase				
Period			Titration	Maintenance			
Visit		1	2	3	4	5	6
Day	-56	-7 to 1	0	7	35	63	91
Treatment	NO AEDs for 90 days		Placebo or gradual titration to OXC 1200 mg/day				
	↑ randomization						

Titration period for OXC/placebo began on Visit 2. Patients randomized to OXC treatment were started on an initial OXC dose of 600 mg/day (300 mg bid) on days 1 and 2 and were titrated to 900 mg/day (450 mg bid) on days 3 and 4 and 1200 mg/day (days 5 and 6). Patients randomized to the placebo treatment received matching placebo tablets throughout the double blind phase. The maintenance period lasted for 84 days during which patients received OXC 1200 mg/day or placebo. Patients who were unable to tolerate the 1200 mg/day OXC dose were allowed to have their dose decreased to 900 mg/day at Visit 3 only.

Blood samples were collected at Visits 3 to 6 for population pharmacokinetic-pharmacodynamic analysis of plasma levels of OXC and MHD. Patients were required to record the time of their last 3 doses and the time of their last meal prior to the visit. To ensure that blood samples were collected evenly during the visit, the 8:00 am to 6:00 pm time period was divided into 3 time slots (8:00 am to 11:00 am, 11:01 am to 2:00 pm, 2:01 pm to 6:00 pm). Patients were required to report for their blood draws at each of the 3 time slots (in any order) at least once during visits 3-6. The purpose of the schedule was to distribute blood samples over the drug absorption and elimination phases. At one center, blood samples were collected (Visits 3-6) just before the morning dose for determination of trough concentrations of OXC and MHD.

Non linear mixed effects models were fitted to the plasma concentrations of MHD using NONMEM Version 4. The analysis procedure for the pharmacokinetic model was similar to that described in the section above.

To explore pharmacokinetic-efficacy relationships,  $C_{min}$  was used as an explanatory variable in regression models for the primary outcome – time to first seizure. The models fitted to the data were of the form:  $\text{Log } \lambda(t) = a_0 + \beta_1 \text{SEIZB\_28} + \beta_2 \text{TRT} + \beta_3 C_{min}$ , where,  $\lambda(t)$  is the hazard rate for the time to first seizure at time  $t$ , SEIZB\_28 is the 28-day baseline seizure frequency, TRT is the treatment group (placebo=0 or OXC 1200 mg/day=1),  $a_0$  is the natural logarithm of the baseline hazard (hazard rate for a hypothetical patient with SEIZB\_28 =  $C_{min}$  = TRT =0) and  $\beta_0, \beta_1, \beta_2, \beta_3$  are regression parameters.

Safety outcomes for which relationships with plasma concentrations were explored included adverse events (AEs) and abnormalities in clinical laboratory assessments with incidences greater than 10%. The AEs that were included were dizziness, headache, nausea, upper respiratory infection, fatigue and viral infection. Clinical laboratory variables were not included as their incidence did not exceed 10%. Relationships between C<sub>min</sub> and the AEs were explored.

Pharmacokinetic analysis was performed only for MHD, the active metabolite of OXC. The final population pharmacokinetic model contained a combined residual error model and one random effect for apparent clearance (C<sub>l/F</sub>). "Visit" and creatinine clearance were found to be the covariates significantly affecting C<sub>l/F</sub>. The addition of other covariates to the final model were not significant. Following 600 mg bid OXC, the average MHD clearance for was 2.35 L/hr and the average estimated C<sub>min</sub> was 15.2 mg/L. In comparison, in healthy volunteers following a 300 mg bid dose, the average MHD clearance was 2.2 L/hr and the average C<sub>min</sub> was 5.2 mg/L. The results suggest that the pharmacokinetics of MHD in epileptic patients was not significantly different from those in healthy volunteers. Also, the population estimate for C<sub>l/F</sub> in adults from this study was similar to the estimate obtained in children in an earlier study (2.33 L/h). The apparent clearance of MHD appeared to be related to the creatinine clearance. For e.g., the apparent clearance of MHD for a patient with a creatinine clearance of 50 ml/min was 0.7 time (or 30% lower) than a patient with the typical creatinine clearance of 100 ml/min. This finding is consistent with a Phase 1 study in renally impaired patients which suggested that apparent clearance for MHD is related to renal function. The analysis did not reveal any significant associations between efficacy outcomes and treatment group or pharmacokinetic variables. The applicant attributes this lack of significance to the small sample size. Overall, there was no evidence of relationship of MHD pharmacokinetics to any of the safety related events.

**SPECIAL POPULATIONS**

**PEDIATRICS**

- What is the pharmacokinetic behavior of OXC in special populations (children, renally impaired and hepatically impaired)?
- Do any of these special populations require an adjustment in their initial dosage regimens?

Single dose pharmacokinetics following doses of 5 or 15 mg/kg of OXC in children treated with upto 3 epileptic drugs: The study was an open label, single dose study in 2 – 12 year old polymedicated epileptic (partial or generalized seizures) children. The children were divided into 2 age groups: 2-5 years (n=13) and 6-12 (n=18) years. In the 2 age groups, the patients were randomized to receive a single dose of either 5 mg/kg or 15 mg/kg OXC orally. The study population consisted of 34 epileptic children. Of these, 31 (18 males and 13 females) were included in the pharmacokinetic analysis.



Mean (SD) PK Parameters for MHD Following A Single Dose Of 5 or 15 mg/kg OXC in Epileptic Children

PK Parameters	Dose = 5 mg/kg		Dose = 15 mg/kg	
	2 - 5 years (n=6)	6 - 12 years (n=7)	2 - 5 years (n=8)	6 - 12 years (n=10)
C <sub>max, obs</sub> (µmol/L) (µmol/kg)	1.13 (0.23)	0.94 (0.17)	0.65 (0.10)	0.69 (0.15)
T <sub>max</sub> (h) as median	3.0	4.0	4.0	4.0
T <sub>1/2</sub> (h)	4.9 (1.6)	6.7 (1.3)	7.2 (2.1)	9.3 (3.8)
AUC <sub>0-∞, obs</sub> (µmol.h/L) (µmol/kg)	9.3 (1.7)	13.0 (3.1)	10.1 (2.7)	14.0 (5.6)
MRT (h)	7.4 (1.5)	11.6 (2.9)	11.7 (2.4)	16.1 (4.7)

$C_{max, spec}$ ,  $AUC_{inf, spec}$  = Specific values of  $C_{max}$  and AUC for a dose unit, i.e. values of  $C_{max}$  and AUC adjusted for the actual dose, divided by the theoretical dose 5 or 15 mg/kg and multiplied by the conversion factor (0.2523) for dose in molar units.

MHD was the main active compound in plasma in children dosed with 5 or 15 mg/kg OXC. OXC concentrations were low; approximately [redacted] of MHD concentrations (similar to adults). The pharmacokinetics of MHD were age-dependant with lower exposures and shorter  $t_{1/2}$  observed in the younger group (2-5 years) compared to the older group (6-12 years). Peak MHD concentrations increased less than proportionally with dose and mean values of  $C_{max, spec}$  decreased significantly with increasing dose in both age groups. This was not observed in adults following single doses of 150, 300 and 600 mg OXC. The lower exposure of MHD observed in the younger children (2-5 years) maybe partly related to faster metabolism in this age group as compared to adults or children between the ages of 6-12 years. The pharmacokinetic parameters for MHD from this study have been compared to those obtained in adults. The mean  $T_{1/2}$  of MHD in children aged 6-12 years receiving 15 mg/kg (9 hours) was similar to that in healthy adults (9-10 hours) following administration of OXC. The mean  $t_{1/2}$  in the age group 2-5 years at both doses and in the age group 6-12 years at the 15 mg/kg dose was lower than that observed in adults. Comparison of the MHD exposure ( $AUC_{inf, spec}$ ) between children and adults showed that the MHD exposure was similar between adults (lowest mean value observed in adults) and children aged 6-12 years; the exposure in children aged 2-5 years was lower.

**Multiple dose pharmacokinetics following treatment with tid (or bid) OXC in children on concomitant anticonvulsant drugs:** The trial was a multicenter study divided in 3 periods: titration, maintenance and follow-up in which epileptic children with upto 3 anticonvulsant drugs received OXC in addition. Children were divided into 2 groups based on age: 2-5 and 6-14 years. Titration period: 2 months, visits 1-4. Each patient received a starting dose of OXC of about 10 mg/kg/day. The dose was then increased progressively in order to obtain satisfactory safety and efficacy. Maintenance Period: 4 months, visits 5-7. Once the optimal dose was determined, patient who showed therapeutic benefit entered this phase. Change of the dosing regimen due to insufficient therapeutic effect and/or poor tolerability was exceptionally allowed. Also, doses greater than 50 mg/kg were exceptionally allowed. Follow-up Period: 1 year, visits 8 and 9. During this long term follow-up period, the dosing regimen could be modified and doses greater than 50 mg/day were exceptionally allowed. Blood samples were collected from visits 1-7 (titration and maintenance) and in some patients at visit 9 (follow-up) in the morning before administration of OXC for the determination of MHD. The study population consisted of 114 epileptic children with partial or generalized tonic-clonic seizures. Children were divided into 2 groups based on age: 2-5 years and 6-14 years. Of these 85 patients were included in the statistical analysis. The mean specific optimal dose in children aged 2-5 years was 38% higher than in children aged 6-14 years. Since the difference is small compared to the range of doses used across age groups, age may be a minor factor for adjustment of the effective dose of OXC. MHD trough concentrations were lower (average of 34%) in younger children compared to the older age group. This indicated a more rapid elimination of MHD in younger children. Concomitant AED's with enzyme inducing properties decreased MHD trough concentrations by 12% and 32% in the younger and older age groups, respectively.

**Multiple dose pharmacokinetics following treatment with tid (or bid) OXC in children treated with upto 2 antiepileptic drugs (after substitution of Tegretol therapy):** The study was an open label trial in 22 children who were being treated with Tegretol for epilepsy. Tegretol was gradually replaced with OXC. During the titration phase (4-8 weeks), the daily dose of OXC was individually adjusted at weekly intervals in order to obtain the maximum therapeutic benefit along with satisfactory tolerability. Once the optimum maintenance dose was identified, the treatment was continued for at least 12 weeks. Blood samples were collected before the morning dose during the titration phase (maximum of 9 samples in weekly intervals) and during the maintenance phase (4 samples in 2-4 week intervals). The maximum therapeutic benefit associated with a satisfactory tolerability was reached in this group of 22 patients with a mean daily OXC dose of 1200 mg  $\pm$  444 mg, resulting in mean steady-state MHD concentrations of 56.8  $\pm$  22.8 nmol/g. The daily dose of OXC increased with increase in patient age and weight. There appeared to be no relationship between the MHD steady-state concentrations and

age/weight in these patients. No relationship between individual average steady-state MHD plasma concentrations versus the daily dose of OXC was identified in this patient population.

**Multiple dose pharmacokinetics following treatment with tid (or bid) OXC (use of OXC as monotherapy):** The trial was a double blind, parallel study comparing OXC and phenytoin (PHT) monotherapy. The trial consisted of a titration period, a maintenance period & a follow-up period. Titration Period: (starting with visit 2, following screening) and a duration of 8 weeks. Patients were randomly assigned to either OXC or PHT (tid regimen: 300 mg OXC or 100 mg PHT). Thereafter, the dose could be adjusted at biweekly visits (visit 3-6). The aim was to achieve a maximum daily dose, defined as the lowest dose that provides complete seizure control at the end of the titration phase (visit 6).

Maintenance Period: Following visit 6, patients entered a 48-week maintenance period. The total daily dose reached at Visit 8 was to be used throughout the maintenance period up to Visit 12. Dose adjustment was permitted only if the patient did not have adequate seizure control or if the patient had tolerability problems. The maximum daily dose was not to exceed 2400 mg OXC or 800 mg PHT, respectively.

Blood samples were collected from the titration period and the maintenance period in the morning before administration of OXC for the determination of MHD and PHT. A total of 194 epileptic children aged 5-18 years participated in the study. The maintenance periods were completed by 73 patients under OXC and by 60 patients under PHT therapy. During the study, 24 patients on OXC and 36 patients on PHT discontinued. In the maintenance period of the treatment with OXC, the doses that were most frequently administered were between 15 and 25 mg/kg. The most frequently observed plasma concentrations were in the range of ————. The plasma levels of MHD increased with dose of OXC. In the maintenance period of the treatment with OXC, the doses that were most frequently administered were between 5 and 7 mg/kg. The most frequently observed plasma concentrations were in the range of ————. Compliance to OXC and PHT was similar in both groups of patients (72% and 68%, respectively, were compliant).

**Proposed dosing regimen in children:** The proposed dosing regimen for children older than 2 years is the same as that proposed in adults: Starting Dose of 8-10 mg/kg/day as 2 divided doses and if clinically indicated, dose may be increased by a maximum increment of 10 mg/kg/day at weekly intervals from the starting dose to a maximum dose of 46 mg/kg/day. The applicant has justified this pediatric dose based on the fact that therapeutic effects were observed at a median maintenance dose of OXC at 30 mg/kg/day as adjunctive therapy. Also, therapeutic benefit was observed in majority of the patients at a maintenance dose of 15-25 mg/kg/day in a monotherapy trial with OXC.

The systemic exposure to MHD was reduced in children compared to adults given the same dosing regimen. In children aged 2-6 years, the mean specific trough concentration was about 50 to 60% lower than in adults; in children aged 6-14 years, the mean specific trough concentration was about 30 to 40% lower than in adults. Possible reasons for the decreased exposure observed in children compared to adults may be due to:

- a) a difference in the ratio of OXC to MHD in children compared to adults. However, in a single dose study in pediatric patients OXC concentrations were low; approximately 10-15% of MHD concentrations (similar to adults).
- b) differences due to effect of food on MHD exposure (since the current market formulation with food effect was used in these trials). These differences include differences in the type of meals consumed by children compared to adults.

A higher starting dose may be recommended in the pediatric population. Since exposures in children were found to be lower than in adults at comparable doses, the proposed starting dose in these children may be lower than that required for seizure control. It is recommended that the applicant evaluate the pediatric population further in order to recommend an appropriate dosing regimen in this population.

**RENAL IMPAIRMENT:** Plasma and urine kinetics of MHD, OXC (and conjugates) and DHD was studied in patients with impaired renal function following a single oral dose of 300 mg OXC. This was an open label, single dose study of OXC administered as a 300 mg tablet following an overnight fast. This study was conducted in male (20) and female volunteers (6) ranging in age

from 24-77 years, with a body weight from 49 to 89 kg. Subjects were classified into one of 4 groups based on their creatinine clearance:

Group 1: Clcr > 90 ml/min (n=6); healthy subjects; Group 2: Clcr 30 – 80 ml/min (n=6)

Group 3: Clcr 10 – 30 ml/min (n=7) and Group 4: Clcr 2 – 10 ml/min (n=7); not hemodialyzed.

**Mean (SD) Plasma Pharmacokinetic Parameters for Unconjugated MHD, OXC and DHD**

PK parameter,	Group 1:Clcr > 90 ml/min (n=6)	Group 2: Clcr 30 – 80 ml/min (n=6)	Group 3: Clcr 10 – 30 ml/min (n=7)	Group 4: Clcr 2 – 10 ml/min (n=7)
<b>MHD Pharmacokinetics</b>				
Cmax ( $\mu\text{mol/l}$ )	8.6 (0.8)	12.1 (2.3)	13.7 (3.4)	13.0 (2.7)
Tmax (hr); median	4	6	8	6
AUCinf ( $\mu\text{mol.h/l}$ )	203 (37)	337 (74)	502 (167)	491 (113)
T1/2 (hr)	10 (1)	12 (2)	16 (5)	19 (3)
<b>OXC Pharmacokinetics</b>				
Cmax ( $\mu\text{mol/l}$ )	1.23 (0.45)	1.67 (0.90)	1.45 (0.59)	1.82 (1.50)
Tmax (hr); median	1.5	2	2	2
AUC0-168 ( $\mu\text{mol.h/l}$ )	4.2 (1.3)	7.9 (4.6)	9.2 (5.5)	8.3 (3.2)
<b>DHD Pharmacokinetics</b>				
Cmax ( $\mu\text{mol/l}$ )	0.18 (0.04)	0.34 (0.07)	0.48 (0.13)	0.49 (0.20)
Tmax (hr); median	12	24	48	42
AUC0-168 ( $\mu\text{mol.h/l}$ )	4.8 (3.0)	24.8 (12.9)	44.0 (16.5)	51.4 (23.7)

Peak plasma MHD concentrations in patients with impaired renal function were higher than those in normal volunteers. The half-life for MHD increased with degree of renal impairment, with the longest mean terminal half-life for Group 4. The MHD exposure was 1.5 times greater for Group 2 compared to Group 1 and approximately 2.5 times greater for Groups 3 and 4 compared to Group 1. Exposure to MHD and peak MHD concentrations were similar for Groups 3 and 4. OXC exposure was approximately 2-fold greater in patients with renal impairment compared to normal volunteers. The influence of renal impairment on the plasma levels of DHD was marked. In subjects with normal renal function, maximum plasma DHD concentrations were reached approximately 12 hours post-dose. For patients with impaired renal function, maximum plasma MHD concentrations following dosing were reached after 24 hr for Group 2, 48 hours for Group 3 and 42 hours for Group 4. Peak plasma DHD concentrations in patients with impaired renal function were 2.5 fold greater than those in normal volunteers. The DHD exposure was 5-6 fold greater for Group 2 compared to Group 1 and approximately 10 fold greater for Groups 3 and 4 compared to Group 1. Exposure to DHD and peak DHD concentrations were similar for Groups 3 and 4. The results suggest that oxidation of MHD to DHD was enhanced in patients with renal impairment, suggesting that metabolism by the liver may compensate for renal impairment.

The relationship between the exposure to MHD, OXC and DHD following OXC administration and creatinine clearance was explored. Results suggested that MHD and DHD exposures are increased in subjects with low serum creatinine clearance values. The concentrations of conjugated MHD and OXC were expressed as the difference between concentrations determined before and after hydrolysis. For DHD, the total concentrations measured after hydrolysis was similar to those of the unconjugated compound, indicating that the concentrations of conjugated DHD were low.

**Mean (SD) Plasma Pharmacokinetic Parameters for Conjugated MHD, OXC and DHD**

PK parameter	Group 1:Clcr > 90 ml/min (n=6)	Group 2: Clcr 30 – 80 ml/min (n=6)	Group 3: Clcr 10 – 30 ml/min (n=7)	Group 4: Clcr 2 – 10 ml/min (n=7)
<b>MHD Pharmacokinetics</b>				
Cmax ( $\mu\text{mol/l}$ )	2.1 (0.7)	4.4 (2.8)	10.8 (3.4)	19.9 (6.7)
Tmax (hr); median	8	10	32	32
AUCinf ( $\mu\text{mol.f/l}$ )	48.7 (9.9)	176 (138)	731 (342)	1770 (914)
T1/2 (hr)	13 (3)	14 (5)	24 (9)	42 (25)
<b>OXC Pharmacokinetics</b>				
Cmax ( $\mu\text{mol/l}$ )	1.3 (0.7)	2.2 (0.8)	4.1 (3.3)	5.5 (2.1)
Tmax (hr); median	1.5	4	8	10
AUC0-168 ( $\mu\text{mol.h/l}$ )	11.2 (4)	35.8 (18.7)	149 (107)	298 (77)
T1/2 (hrs)	-	18 (6)	16 (6)	43 (18)

In subjects with normal renal function, the mean AUC for conjugated MHD was 4 times lower than that of the unconjugated MHD. However, in patients with moderate and severe renal impairment (Group 4), the mean AUC for conjugated MHD was approximately 2 and 4 times higher, respectively, than that of the unconjugated MHD. The mean AUC of conjugated OXC were 3 and 36 times those of the unchanged drug for normal and severely impaired subjects, respectively. The half-life of the conjugated compounds was increased 2-3 fold in patients with severe renal impairment. These results suggest that the glucuronides of MHD and OXC are likely to accumulate in patients with impaired renal function during chronic OXC therapy. It is possible that regeneration of MHD from its conjugates could be higher after multiple doses compared to that after a single dose, especially in patients with severe renal impairment.

Mean (SD) Urine Pharmacokinetics of MHD, OXC and DHD

Group	72-hr Urinary Excretion (Percent of Dose) as Mean (SD)				
	MHD		OXC		DHD
	Unconjugated	Conjugated	Unconjugated	Conjugated	Unconjugated
1 Clcr > 90 ml/min (n=6)	21 (4)	34 (9)	< 0.05	6 (1)	2 (1)
2 Clcr 30 - 80 ml/min (n=6)	18 (10)	38 (10)	< 0.05	6 (2)	3 (2)
3 Clcr 10 - 30 ml/min (n=7)	7 (2)	39 (13)	< 0.05	7 (4)	0.7 (0.3)
4 Clcr 2 - 10 ml/min (n=7)	6 (4)	21 (9)	< 0.05	3 (2)	0.4 (0.3)

MHD and its glucuronides were the major compounds recovered in urine over 72 hours. The recovery of unconjugated MHD was 3 fold lower in patients with Clcr < 30 ml/min. The recovery of conjugated MHD was similar for Groups 1, 2 and 3, but was slightly lower in patients with Clcr < 10 ml/min. The urinary recoveries of MHD and its glucuronides in normal subjects in this study were slightly lower than those found in 2 volunteers after administration of a single oral dose of 14C-labelled OXC. The urinary excretion of MHD glucuronides was almost complete at 72 hours in normal volunteers and patients with mild renal impairment; however, it was not complete in patients with moderate and severe renal impairment. The renal clearance of MHD and its conjugates decreased with decreasing renal function (creatinine clearance). The increase in plasma half-life of unconjugated MHD in renally impaired patients was low in comparison to the marked reduction in its renal clearance. This is probably because of the high contribution of non-renal elimination processes for MHD. OXC was detected in trace amounts in urine. The recovery of DHD in urine was also low and decreased with decreasing creatinine clearance. For DHD, the total concentrations measured after hydrolysis was similar to those of the unconjugated compound, indicating that the concentrations of conjugated DHD were low.

The recommended dose of OXC to be administered in patients with renal impairment was based on the ability to maintain the same steady state MHD concentrations in these patients as in normal subjects. The dose was calculated as the ratio of the total MHD exposure (AUC<sub>inf</sub>) in patients to normals. The dose for patients with Clcr 30-80 ml/min = 70% of the normal dose and the dose for patients with Clcr 2-30 ml/min = 50% of the normal dose. The treatment with OXC in epilepsy is gradually built up in order to achieve the minimally effective dose for the individual patient. Based on this, the applicant does not recommend a dosage adjustment in patients with Clcr of 30-80 ml/min. For patients with Clcr < 30 ml/min, a dose reduction of 50% is recommended at the beginning of the titration period, dose increases should be reduced by 50% compared to patients with normal renal function. The dosing recommendation in renally impaired patients is acceptable.

**HEPATIC IMPAIRMENT:** The effects of different degrees of hepatic impairment (HI) on the pharmacokinetics and metabolism of OXC and MHD was evaluated in normal subjects and in subjects with impaired hepatic function. This was an open label, multicenter, single dose trial in which 900 mg (3x300 mg) of OXC was administered to healthy volunteers and hepatically impaired patients. Based on their individual degree of hepatic function, subjects were stratified using the Child-Pugh system to one of 3 groups: Group 1: normal hepatic function, Group 2:

mild HI (Child-Pugh classification A) and Group 3: moderate HI (Child-Pugh classification B). The study was conducted in 26 males ranging in age from 40 to 65 years, 12 with normal hepatic function, 7 with mild HI and 7 with moderate HI. Of these, pharmacokinetic evaluations were performed in 6 healthy volunteers, 7 mildly impaired and 6 moderately impaired patients. OXC was administered following administration of a standardized breakfast.

#### Mean (SD) MHD Plasma Pharmacokinetic Parameters

PK Parameter	Group 1 (n=6) Normal	Group 2 (n=7) Child-Pugh A	Group 3 (n=6) Child-Pugh B
AUC <sub>0-24</sub> (μmol.h/l)	1094.3 (274.7)	1189.1 (185.4)	1026.8 (148.1)
AUC <sub>inf</sub> (μmol.h/l)	1112.5 (272.5)	1207.9 (189.7)	1044.3 (148.7)
C <sub>max</sub> (μmol/l)	41.2 (8.8)	43.6 (4.4)	35.8 (3.2)
T <sub>max</sub> (h)	8 (median)	8 (median)	10 (median)
T <sub>1/2</sub> (hr)	10.4 (1.8)	10.5 (1.2)	12.2 (1.3)

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#### Mean (SD) DHD Plasma Pharmacokinetic Parameters

PK Parameter	Group 1 (n=6) Normal	Group 2 (n=7) Child-Pugh A	Group 3 (n=6) Child-Pugh B
C <sub>max</sub> (μmol/l)	1.0 (0.5)	0.4 (0.3)	0.4 (0.5)
T <sub>max</sub> (h)	24 (median)	24 (median)	24 (median)

There were no statistically significant differences in the AUC and C<sub>max</sub> for MHD between normal volunteers and subjects with mild or moderate HI. DHD levels were close to or below the limit of quantitation for most subjects at several time points; therefore, no other pharmacokinetic parameters were calculated for DHD in plasma. For DHD, the difference in C<sub>max</sub> between normals and hepatically impaired subjects was statistically significant (lower). The baseline hepatic function classification on the C<sub>max</sub> for DHD was statistically significant.

90% confidence intervals for the ratios of AUC and C<sub>max</sub> (for MHD) between mildly impaired and moderately impaired groups and for the normal subjects were estimated. The results suggest that in patients with mild HI, the MHD exposure and peak MHD plasma concentrations were slightly higher than those in patients normal hepatic function. There did not appear to be any differences between patients with moderate hepatic impairment and normal volunteers.

Parameter	Pairwise comparison	Ratio	90% CI
AUC <sub>0-24</sub> (μmol.h/l)	Child Pugh A (mild) vs Normal	1.105	(0.92, 1.33)
	Child Pugh B (moderate) vs Normal	0.957	(0.79, 1.16)
C <sub>max</sub> (μmol/l)	Child Pugh A (mild) vs Normal	1.075	(0.93, 1.24)
	Child Pugh B (moderate) vs Normal	0.884	(0.76, 1.03)

#### Mean (SD) Urine Pharmacokinetics for MHD

Parameter	Compound	Normals (n=6)	Child-Pugh A (n=7)	Child-Pugh B (n=6)
Ae (0-120 h) (% of dose)	Free MHD	17.0 (14.1)	27.6 (17.1)	19.5 (8.3)
Ae (0-120 h) (% of dose)	Conjugated MHD	22.4 (4.1)	23.6 (8.7)	14.7 (7.6)
Ae (0-120 h) (% of dose)	Total MHD	39.4 (16.0)	51.2 (24.6)	34.2 (15.5)
Renal Clearance (L/h)	Free MHD	0.51 (0.32)	0.85 (0.58)	0.69 (0.34)

#### Mean (SD) Urine Pharmacokinetics for DHD

Parameter	Compound	Normals (n=6)	Child-Pugh A (n=7)	Child-Pugh B (n=6)
Ae (0-120 h) (% of dose)	Free DHD	1.6 (1.3)	1.5 (1.3)	1.1 (1.4)
Ae (0-120 h) (% of dose)	Total DHD	2.3 (0.9)	2.0 (1.1)	1.4 (2.2)

The amounts of free, conjugated and total MHD excreted in the first 120 hours after dosing (Ae<sub>0-120</sub>) were expressed as a percent of the dose. The urinary excretion of free, conjugated and total MHD was similar for all three groups. The urinary excretion rates were also similar across groups. There were no significant differences in the renal clearance of MHD between the 3 hepatic function groups. For DHD, the urinary excretion of free and total DHD tended to decrease with the severity of hepatic impairment, however, the interindividual variability was high.

There were no significant effects of mild and moderate HI on the pharmacokinetics and metabolism of MHD following a single oral dose of OXC 900 mg. OXC is reduced to MHD which is then primarily conjugated by glucuronidation. Both of these processes did not appear to be affected by mild or moderate HI. For DHD, the difference in C<sub>max</sub> between normals and hepatically impaired subjects was statistically significant (C<sub>max</sub> lower in HI). MHD is oxidatively metabolized to DHD; this process is probably affected by HI. However, DHD is a minor metabolite and is pharmacologically inactive. Therefore the differences in C<sub>max</sub> for DHD are probably not clinically significant. No dosage adjustment is required in subjects with mild or moderate HI. The pharmacokinetics of MHD and DHD have not been evaluated in subjects with severe HI.

#### **METABOLISM**

- Based on metabolic pathways (from in-vitro and/or in-vivo studies), what kind of drug interactions are expected?
- Does OXC have the ability to inhibit or induce any metabolic pathways?
- Does OXC coadministration affect the pharmacokinetics of any of the coadministered drug(s) requiring a dosage adjustment for the coadministered drug(s)?
- Do(es) any coadministered drug(s) affect the pharmacokinetics of OXC requiring a dosage adjustment for OXC?

#### **IN-VITRO METABOLISM**

**In-vitro inhibition of CYP P450 enzymes:** In-vitro experiments to determine the inhibitory potency of OXC and MHD (on CYP 450 enzymes) were conducted by measuring the activity of each P450 enzyme in human liver microsomes in the presence and absence of each compound. Inhibitory constants (K<sub>i</sub>'s) were determined for OXC and MHD following P450 enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP 3A4/5, CYP 4A9/11. OXC and MHD were tested as both competitive inhibitors and non-competitive inhibitors of human P450 enzymes.

Evaluation of OXC and MHD as competitive inhibitors of P450 was done with human liver microsomes pooled from 5 individuals or with liver microsomes from an individual with high levels of the enzyme of interest. The final concentration of OXC and MHD used in the experiments were 0, 10, 100, 200 and 300  $\mu$ M (based on the fact that C<sub>max</sub> in humans for OXC is 5  $\mu$ M and that for MHD is approximately 50  $\mu$ M following a 1200 mg dose of OXC). The concentration of each marker substrate used was K<sub>m</sub> and 4xK<sub>m</sub>. Kinetic parameters (K<sub>m</sub> and V<sub>max</sub>) for each P450 activity were determined in the microsome sample that was used in the inhibition study. Reactions were initiated by the addition of NADPH.

Evaluation of OXC and MHD as non-competitive inhibitors of P450 was done with human liver microsomes that were preincubated with OXC or MHD and NADPH for 10 minutes to allow for the generation of metabolites that could inhibit CYT P450 non competitively. Following the 10 minute incubation, the marker substrate was added and the incubation continued to measure any residual P450 activity. The concentration of OXC and MHD to be used in these experiments was determined from the competitive inhibition experiments. The concentration that corresponds to the highest concentration of OXC and MHD that caused no more than 20% inhibition of the P450 enzyme being studied. The concentration of the marker substrate was equal to K<sub>m</sub>. These experiments were performed at a single concentration of OXC and MHD and a single concentration of the marker substrate, therefore, K<sub>i</sub> could not be determined for non-competitive inhibition. The experiment also involved a single pre-incubation period (10 minutes), hence the possibility of OXC or MHD causing a time-dependant inactivation of P450 enzymes could not be determined.

The applicant has attempted to make in vitro to in vivo extrapolations from the data generated. The ratio of plasma C<sub>max</sub> and the K<sub>i</sub> value was used as a crude predictor of in vivo drug interactions. The applicant has assumed that C<sub>max</sub>/K<sub>i</sub> ratios that are substantially below unity

are not likely to be clinically relevant, and as this ratio approaches or increases beyond unity, the potential for drug interactions increases.

Results from these experiments suggested that OXC and MHD have little capacity to inhibit most of the P450 enzymes with the exception of CYP 2C19 and CYP 3A4/5. Both OXC and MHD were observed to competitively inhibit CYP 2C19 with  $K_i$  values of 228  $\mu\text{M}$  and 88  $\mu\text{M}$ , respectively. CYP 3A4/5 was found to be inhibited both by OXC (non-competitive) and MHD (competitive) at  $K_i$  values of 279  $\mu\text{M}$  and 647  $\mu\text{M}$ , respectively. The mean steady state trough plasma concentrations of MHD following 1200 mg bid dose of OXC is approximately 108  $\mu\text{M}$  in patients and  $C_{\text{max}}$  following a 1200 mg dose was approximately 50  $\mu\text{M}$ . Comparing these pharmacokinetic parameters to the  $K_i$  values suggest that while inhibition of CYP 3A4/5 by OXC and MHD may not have clinical significance, the inhibition of CYP 2C19 substrates by OXC and MHD may be clinically relevant.

**OXC & MHD as competitive inhibitors of P450 enzymes in human liver microsomes**

P 450 enzyme	P 450 activity	Competitive Inhibition by OXC		Competitive Inhibition by MHD	
		$K_i$ ( $\mu\text{M}$ )	$C_{\text{max}} / K_i$	$K_i$ ( $\mu\text{M}$ )	$C_{\text{max}} / K_i$
CYP 1A2	7-Ethoxyresorufin O-dealkylase	1150	0.0043	> 1350	0.037
CYP 2A6	Coumarin 7-hydroxylase	> 1350	< 0.0037	> 1350	0.037
CYP 2C9	Tolbutamide methyl-hydroxylase	> 1350	< 0.0037	> 1350	0.037
CYP 2C19	S-mephenytoin 4'-hydroxylase	228	0.022	88.3	0.57
CYP 2D6	Dextromethorphan O-demethylase	> 1800	< 0.0028	> 1800	0.028
CYP 2E1	Chlorzoxazone 6-hydroxylase	> 900	< 0.0056	> 900	0.056
CYP 3A4/5	Testosterone 6-hydroxylase	270	0.019	647	0.077
CYP 4A9/11	Lauric Acid 12-hydroxylase	> 1350	< 0.0037	> 1350	0.037

$C_{\text{max}}$  for OXC = 5  $\mu\text{M}$ ;  $C_{\text{max}}$  for MHD = 50  $\mu\text{M}$

**In-vitro induction of CYP P450 enzymes:** The effects of OXC, MHD and DHD on CYP P450 enzymes was studied in vitro using human hepatocytes. Phenobarbital and rifampicin were used as reference compounds. OXC, MHD and DHD at concentrations of 50 and 200  $\mu\text{M}$  and phenobarbital at 3000  $\mu\text{M}$  and rifampicin at 50  $\mu\text{M}$  were incubated with adult female human hepatocytes in primary culture. Induction by OXC and MHD of Ethoxyresorufin O-dealkylase (EROD) and pentoxyresorfin O-dealkylase (PEROD), two CYP dependant drug metabolizing enzyme activities were evaluated. Also, methylumbelliferone conjugation with glucuronic acid was studied to evaluate the inductive effects of OXC and MHD on Phase 2 glucuronidation.

A 3.2 fold decrease in EROD activity was found during the 72-hour incubation period in the control cultures. In comparison, 69% and 60% increases were observed with DHD (at 200  $\mu\text{M}$ ) and rifampicin, respectively. A 1.6 fold decrease in PEROD activity was found during the 72-hour incubation period in the control cultures. In comparison, approximately a 30-34% increase was observed with OXC (at 50 and 200  $\mu\text{M}$ ) and phenobarbital. UDP-glucuronyltransferase activity was well maintained throughout the 72-hour incubation period. It was increased 1.2 to 1.5 fold by all test compounds as well as the reference substances. The highest increase obtained was observed with OXC (47%). MHD and DHD showed lower effects (22% and 39%, respectively).

To summarize, these results showed that EROD activity (CYP activity) was slightly increased after a 72-hour exposure to DHD, compared to control cultures and UDP-glucuronyltransferase activity was induced by OXC, DHD and MHD.

**IN-VIVO METABOLISM:** Studies with carbamazepine (CBZ) have shown that there is a change in antipyrine kinetics during CBZ treatment, suggesting enzyme induction by CBZ. Since OXC is an analog of CBZ, this trial was aimed at obtaining additional information on the hepatic oxidative enzyme inducing potential of OXC in a population maintained at a high daily dosage of OXC. Antipyrine was used as a marker to determine the oxidizing capacity of CYP P450 enzymes.

**A pharmacokinetic study on the enzyme-inducing capacity of OXC was conducted in healthy males following multiple, oral doses.** The study was an open label study with 3 sequential treatments given to each subject. Treatment A=1x600 mg antipyrine given orally;

Antipyrine was used as an exogenous measure of hepatic activity; Treatment B=1x300 mg OXC given orally; Treatment C=1x300 mg OXC q12h for a total of 29 doses. In addition, subjects received a single 600 mg oral dose of antipyrine on days 8 and 15 of this treatment. There was a washout period of at least 2 days between treatments A and B, and 6 days between treatments B and C.

Mean (SD) Pharmacokinetic Parameters following single and multiple doses of OXC (n=8)

PK Parameters	OXC		MHD		DHD	
	Single dose	steady-state	Single dose	steady-state	Single dose	steady-state
$C_{max}$ ( $\mu\text{g/g}$ )	2.7 (1.3)	4.1 (1.7)	13.0 (3.9)	38.2 (6.1)	N/a	2.9 (1.8)
$T_{max}$ (h)	2.0	1.5	6.0	2.0	N/a	2.0
$K_e$ (1/hr)	N/a	N/a	0.085 (0.015)	0.059 (0.018)	N/a	N/a
AUC ( $\mu\text{g}\cdot\text{h/g}$ )	8.0 (5.7)	14.1 (6.4)	256 (59)	395 (59)	N/a	23.1 (14.8)

Comparison of pharmacokinetic parameters following a single dose of OXC to those following multiple doses of OXC showed that the exposure to OXC and MHD were increased by 76% and 55%, respectively, at steady state. Peak plasma concentrations for MHD and OXC also increased 2-3 fold following multiple doses of OXC. However,  $T_{max}$  for all 3 compounds decreased following multiple doses. Analysis of plasma trough concentrations of MHD showed that steady state was achieved before the final dose of OXC (at approximately 50 hours post-dose). Comparison of predicted steady-state concentrations of MHD to those observed suggested that in all subjects predicted values were lower than those observed. However, the predicted time to reach steady-state was similar to what was observed.

Salivary antipyrine concentrations were used to calculate elimination rates for antipyrine following treatment A (antipyrine alone), treatment C (on days 8 and 15 of dosing), and post-study. There were no significant differences between the antipyrine elimination rates across treatments. There were no significant effects of OXC on the concentrations of other enzymatic markers studied in this trial. There was no consistent change in the urinary elimination of 6-hydroxy cortisol during treatment C or a 2 weeks post-study. There were no significant changes in the serum levels of most of the hormones between baseline values and those obtained during treatment C and post-study. Prolactin concentrations were elevated during treatment C and post-study compared to baseline.

Based on the data obtained from this study, the applicant concludes that OXC does not induce its own metabolism (since the elimination rate constants were similar for single and multiple doses). However, concentrations of OXC and MHD at steady state were higher than expected from the data after a single dose of OXC. The applicant attributes this increase after multiple dosing to the effect of food on OXC and MHD pharmacokinetics. OXC was administered in the fasted state following a single dose; however no recommendations were made with regard to food for the multiple dose phase of the study. Based on the assumption that subjects were administered OXC with food during the multiple dose phase, the applicant attributes the greater than expected steady state concentrations to the effect of food on systemic bioavailability. Since the elimination rate was unchanged between single and multiple dosing, a reason for the decreased clearance of OXC and MHD following multiple doses maybe due to a decrease in the volume of distribution at steady state. (Note: The formulation that was used in this study has not been reported. For the non film coated tablet formulation of OXC, a food effect on systemic bioavailability of MHD was shown. An increase in MHD exposure of 11-39% and a mean increase in OXC exposure of 18% was observed with a high fat meal. In this study, the average increase in MHD and OXC exposure following multiple doses was 55% and 76%, suggesting that the accumulation at steady-state may not be completely attributed to the effect of food.)

An open label within-volunteer single center pharmacokinetic trial was conducted in healthy volunteers to evaluate the hepatic oxidative enzyme inducing potential of OXC after fixed titration and maintenance period at 1800 mg daily. The study was an open label,

single center, within-volunteer trial consisting of 2 periods: a treatment period and a treatment-free period.

**Treatment Period:**

Day 1: Subjects received a single dose of 18 mg/kg oral antipyrene only (baseline; visit 1);

Days 2-13: Subjects received 300 mg qd OXC on days 2-3, 300 mg bid OXC on days 4-5; 450 mg bid on days 6-7; 600 mg bid on days 8-10 and 750 mg bid on days 11-13;

Day 14: Subjects reached the maintenance dose of 900 mg bid OXC (visit 2);

Day 21: Subjects come in for visit 3;

Day 14-35: Subjects continued with the maintenance dose of 900 mg bid OXC. At the end of the maintenance period, on Day 35, subjects received a single dose of 18 mg/kg oral antipyrene (visit 4).

Treatment-free period: consisted of 4 weeks. At the end of 4 weeks of no treatment, subjects received a single dose of 18 mg/kg oral antipyrene only (visit 5).

300 mg uncoated tablets of OXC (formulation f4, batch number 003400) were used.

**Mean (SD) Pharmacokinetic Parameters for Antipyrene (n=13)**

Parameters	Visit 1 Before treatment with OXC	Visit 4 During treatment with OXC	Visit 5 After treatment with OXC
Body weight (kg)	67.4 (6.6)	67.4 (6.6)	67.4 (6.6)
C <sub>max</sub> (µg/g)	25.4 (4.9)	24.1 (4.1)	25.4 (6.2)
T <sub>max</sub> (h)	2	1	1
T <sub>1/2</sub> (hr)	10.8 (3.2)	8.7 (2.1)	10.6 (3.2)
AUC <sub>0-24</sub> (mg.h/L)	316.7 (86.9)	244.3 (58.1)	316.9 (91.2)
AUC <sub>∞</sub> (mg.h/L)*	418.2 (147.6)	293.3 (92.0)	413.2 (146.4)

\* For visits 1 and 5, the extrapolated area to calculate AUC<sub>∞</sub> was > 20%.

The applicant has compared the half-life and AUC of antipyrene during treatment with OXC to those before and after treatment with OXC. The following ratios of the half-life (and AUC) of antipyrene were determined: Visit 4/Visit1, Visit4/Visit5, Visit 1/Visit 5. The estimated ratios were determined by fitting a general linear model to antipyrene half-life (AUC) on a log scale. The model included subject effect and treatment effect (before OXC, during OXC and after OXC). The 95% CI of the ratios were also calculated.

Comparison	Difference in means		P-value		Ratio		95% CI	
	T <sub>1/2</sub>	AUC <sub>∞</sub>	T <sub>1/2</sub>	AUC <sub>∞</sub>	T <sub>1/2</sub>	AUC <sub>∞</sub>	T <sub>1/2</sub>	AUC <sub>∞</sub>
Visit 4/Visit1 During vs Before	-0.20	-0.42	0.03	0.0001	0.82	0.66	(0.69, 0.98)	(0.55, 0.79)
Visit 4/Visit 5 During vs. After	-0.18	-0.32	0.05	0.0013	0.84	0.73	(0.70, 1.00)	(0.61, 0.87)
Visit 1/Visit 5 Before/After	0.02	0.10	0.82	0.27	1.02	1.11	(0.86, 1.21)	(0.92, 1.33)

The results suggest that the antipyrene half-life was decreased during treatment with OXC when compared to before (or after) treatment with OXC. OXC had an effect on antipyrene half-life in reducing it by 22%. Similar findings were observed with the effects of OXC on antipyrene exposure. The results revealed a statistically significant decrease in antipyrene half-life of 22% during administration of daily doses of 1800 mg. Treatment with OXC (1800 mg/day) has a moderate inducing effect on the P450 enzyme system. Comparison of trough levels of OXC and MHD during the different treatment periods suggest that there is no significant autoinduction in the metabolism of OXC following repeated doses of OXC.

An open label, placebo controlled trial was conducted to determine the effects of 900 mg bid OXC on markers of enzyme induction in healthy males (nifedipine and antipyrene were used as markers). The study was an open label, single center, placebo controlled trial. The elimination half-lives of the enzyme markers, nifedipine and antipyrene, were determined prior to dosing with OXC/placebo on Days 1 and 3, respectively. On Day 5, subjects received a single 600 mg dose of OXC/placebo following a standard breakfast. From Day 12, subjects took OXC/placebo according to a fixed titration schedule. The titration period of 13 days consisted of: Days 12-15: 300 mg bid OXC; Days 16-19: 600 mg bid OXC; Days 20-23: 750 mg bid OXC.

Following the titration period, subjects took 900 mg bid OXC for 16 days (days 24-39) and a single dose of 900 mg OXC on day 40. 300 mg uncoated tablets of OXC were used.

Mean (SD) Pharmacokinetic Parameters for Nifedipine (n=27)

Parameter	Day 1 Before treatment with OXC/Placebo		Day 36 During treatment with OXC/Placebo		Day 62 After treatment with OXC/Placebo	
	OXC	Placebo	OXC	Placebo	OXC	Placebo
Cmax (ng/ml)	113 (83)	121 (93)	86 (54)	161 (140)	87 (47)	96 (78)
Tmax (hr)	1.0	1.0	1.0	1.0	1.0	1.5
AUC(0-t) (ng.h/ml)	272 (124)	313 (162)	206 (82)	321 (176)	240 (94)	295 (189)
AUC(0-∞) (ng.h/ml)	281 (129)	336 (178)	213 (84)	339 (191)	250 (103)	325 (226)
CVF (L/h)	90.2 (47.1)	77.3 (47.4)	110 (48.8)	79.5 (47.9)	92.5 (34.8)	97 (92.4)
T1/2 (hr)	2.4 (0.6)	2.8 (0.6)	2.2 (0.5)	2.7 (0.4)	2.3 (0.6)	2.9 (0.8)

Mean (SD) Pharmacokinetic Parameters for Antipyrine (n=27)

Parameter	Day 1 Before treatment with OXC/Placebo		Day 38 During treatment with OXC/Placebo		Day 64 After treatment with OXC/Placebo	
	OXC	Placebo	OXC	Placebo	OXC	Placebo
Cmax (ng/ml)	11.1 (1.3)	11.5 (1.7)	10.6 (1.4)	11.3 (1.8)	11.1 (1.0)	11.8 (2.4)
Tmax (hr)	1.0	1.0	1.0	1.0	1.0	1.0
AUC(0-t) (ng.h/ml)	179 (32)	175 (38)	135 (32)	185 (53)	164 (34)	188 (62)
AUC(0-∞) (ng.h/ml)	192 (37.5)	186 (40.7)	141 (35)	203 (67.4)	175 (42.7)	205 (74.2)
CVF (L/h)	3.24 (0.67)	3.37 (0.74)	4.48 (1.05)	3.26 (1.04)	3.59 (0.89)	3.28 (1.11)
T1/2 (hr)	12.0 (1.7)	11.4 (0.7)	9.5 (1.8)	12.3 (2.9)	11.5 (2.1)	12.4 (2.5)

The applicant has compared the half-life and AUC of antipyrine and nifedipine during treatment with OXC/placebo to those before and after treatment with OXC/placebo. The results from the statistical analysis for antipyrine data suggest that the antipyrine half-life and AUC were different during treatment with OXC when compared to before (or after) treatment with OXC. This difference is probably due to an increase in enzyme activity during intake of OXC. The magnitude of this increase was estimated to be approximately 20%. The nifedipine data did not provide a clear evidence of increased enzyme activity. The variability in the pharmacokinetic parameters was too large to show a statistically significant difference. No changes were observed in the sex hormone levels, SHBG and testosterone. The study results revealed that treatment with OXC (900 mg bid) has a moderate inducing effect on the P450 enzyme system.

**DRUG INTERACTIONS**

**EFFECTS OF COADMINISTERED DRUGS ON OXC**

**Effect of Concomitant Antiepileptic Drugs (CBZ, VPA and PHT) on the Multiple Dose Pharmacokinetics of OXC metabolite, MHD:** The applicant conducted a study to investigate the pharmacokinetic interactions following addition of OXC, as a single dose (600 mg), and after 3 weeks of continuous administration (300 mg tid) to epileptic patients currently treated with multiple (individualized) doses of CBZ, VPA or PHT monotherapy.

Group	Multiple dose AUC <sub>∞</sub> (µg.h/ml) (Geom. Mean and Range)	Ratio and 90%CI for AUC (test A, B,C to reference D)	Multiple dose t1/2 (h) (Geom. Mean and Range)	Ratio and 90%CI for t1/2 (test A, B,C to reference D)
A (CBZ)	71.6 ( )	A/D: 0.60 ( )	11.6 ( )	A/D: ( )
B (VPA)	98.5 ( )	B/D: 0.82 ( )	11.9 ( )	B/D: ( )
C (PHT)	85.5 ( )	C/D: 0.71 ( )	10.8 ( )	C/D: ( )
D (control)	120 ( )		13.0 ( )	

Steady-state MHD concentrations were higher in the control group compared to the other groups. For groups A (CBZ treated) and C (PHT treated), the MHD exposure was significantly lower than the MHD exposure observed in the control group that received OXC alone. The MHD AUC was approximately 40% lower in the CBZ treated group and 30% lower in the PHT treated group. The differences in terminal half-life for MHD were not statistically significant. The applicant suggests